Original article

Tracheal intubation with rocuronium bromide using the 'timing principle' – a comparison with succinylcholine for rapid sequence induction

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Abstract

Background: Rapid sequence induction and intubation aims to secure the airway at the earliest possible time to protect the airway. Succinylcholine is the most popular drug for this but rocuronium is an alternative when succinyl choline is contraindicated. **Aim:** We aimed to compare intubating conditions following intravenous rocuronium bromide (0.6 mg/kg and 1.0 mg/kg) using the *'timing principle'* with that following intravenous succinylcholine hydrochloride (2 mg/kg). **Methods:** Sixty patients, ASA I or II, undergoing elective surgery were randomly assigned to one of three groups: Roc 0.6 (n=20) and Roc 1.0 groups (n=20) received rocuronium 0.6 mg/kg and 1.0 mg/kg respectively and anaesthesia induced at the onset of clinical weakness with thiopentone 5 mg/kg. Sch 2.0 group received thiopentone 5 mg/kg followed by succinylcholine hydrochloride 2.0 mg/kg. Intubating conditions were assessed 60 seconds after administration of thiopentone and were graded as excellent, good or poor. **Results:** Excellent intubating conditions were obtained in 70% of patients in Roc 0.6 and Sch 2.0 groups, and in 55% of patients in Roc 1.0 group. **Conclusion:** Rocuronium bromide administered in a dose of 0.6 mg/kg using the timing principle seems to be a suitable alternative to succinylcholine when a rapid onset of neuromuscular blockade is desired.

Keywords: Rocuronium, succinyl choline, rapid sequence induction, timing principle

Introduction

Rapid sequence induction of anaesthesia and endotracheal intubation is an established technique in patients who are at risk of aspiration of gastric contents during anaesthesia. Succinylcholine hydrochloride synthesised first by Hunt and Javeau in 1911 has a rapid onset of action and produces intense muscle relaxation making it an ideal muscle relaxant for facilitating rapid tracheal intubation.[1] However, succinylcholine has several undesirable properties that contraindicate its use in certain situations. To circumvent this problem, alternative techniques of induction were proposed using nondepolarising neuromuscular blockers which include: priming principle,[2] modified priming technique,[3] high dose technique,[4] or a combination of different neuromuscular blocking agents.[5]

The *'timing principle'*, in which a single bolus of a muscle relaxant is administered before the intravenous anaesthetic, the latter being given as soon as the first clinical signs of muscle relaxation are observed, so that the peak effect of the muscle relaxant and intravenous induction agent may more closely coincide. Of the nondepolarising neuromuscular blocking agents used, rocuronium, is characterised by a rapid onset of neuromuscular blockade and intermediate duration of action. This study was done to evaluate the use of rocuronium employing the *'timing principle'* to produce intubating conditions as an alternative to succinylcholine.

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Patients and Methods

This study was conducted after obtaining departmental dissertation committee approval. Informed and written consent was obtained from each patient. The study design was prospective, randomised and double blind.

Sixty adult patients of either gender (20 in each group), in the age group of 18 to 70 years and scheduled to undergo elective surgery requiring general endotracheal anaesthesia were included in the study. All of them belonged to either grade I or grade II of American Society of Anesthesiologists (ASA) physical status grade and were essentially free from neuromuscular diseases. Those patients who were on medications known to influence neuromuscular function, who had contraindications to the use of succinylcholine hydrochloride, patients in whom difficulty in intubation was anticipated or were at risk of pulmonary aspiration were excluded from the study.

The procedure was explained to the patients on the previous day of surgery and they were informed about the possibility of feeling weak before going to sleep for the surgery. Patients were not premedicated in the ward. On arrival in the operating room, patients were positioned supine and monitoring which included 5-lead electrocardiogram monitoring leads II and V_5, noninvasive blood pressure, pulse oximetry and neuromuscular blockade using train-of-four (TOF) count were established. The limb used for neuromuscular monitoring was shielded from the view of the consultant anaesthesiologist (observer 1) who performed tracheal intubation. Intravenous access was secured with an 18-gauge cannula in the forearm.

Patients were allocated in a randomised fashion to one of three groups as follows: Group 1 (Roc 0.6) – received rocuronium bromide 0.6 mg/kg IV; Group 2 (Roc 1.0) – received rocuronium bromide 1.0 mg/kg IV or Group 3 (Sch) – received succinylcholine hydrochloride 2 mg/kg IV.

All patients received intravenous midazolam 0.02 mg/kg and intravenous fentanyl 1 μg/kg at the start of preoxygenation. Patients were preoxygenated for 3 minutes and 1 mg/kg of intravenous lignocaine was administered through forearm cannula.

Patients allocated to groups 1 and 2 received rocuronium bromide 0.6 mg/kg (or 1 mg/kg respectively) intravenously over 5 seconds through a rapidly running infusion placed in the forearm. Patients were then asked to keep their eyes widely open as long as possible and were closely observed for first signs of weakness, specifically the onset of ptosis (*i.e.*, furrowing of forehead while attempting to open eyes). When this occurred, patients were asked to cough to obtain a gross assessment of their ability to protect the airway. The quality of cough was graded by observer 2 as *normal, weak or absent.*

The time from injection of rocuronium bromide to the onset of clinical weakness (in seconds) was recorded in groups 1 and 2. At the onset of clinical weakness, thiopentone sodium 5 mg/kg was administered intravenously. Neuromuscular monitoring was commenced from the time of loss of eyelash reflex and supramaximal square wave stimuli applied to the ulnar nerve at the wrist at 2 Hz for 2 seconds. This was repeated at 12-second intervals until train of four (TOF) count became 0 and this time was noted. In Roc 0.6 and Roc 1.0 groups, the TOF count at 60 seconds after the administration of thiopentone sodium was recorded along with the time to complete disappearance of the response to TOF stimulation.

Patients in group 3 were treated according to the protocol described for those in groups 1 and 2 with the following changes. A defasciculating dose of vecuronium bromide (0.01 mg/kg) was administered followed 3 minutes later by intravenous thiopentone sodium 5 mg/kg and intravenous succinylcholine hydrochloride 2 mg/kg (administered rapidly over 5 seconds).

Sixty seconds after thiopentone sodium, tracheal intubation was performed by a consultant anaesthesiologist (observer 1) with more than 3 years experience in anaesthesiology who was blinded to the group allocation and, the intubating conditions were assessed according to the following grading scale (*Table 1*). Patients who had a laryngoscopy view of grade III or more were excluded from the study.

Table 1: Assessment of intubation conditions

Variables	Intubation conditions [a]		
	Clinically acceptable		Clinically not acceptable
	Excellent	Good	Poor
Laryngoscopy[b]	Easy	Fair	Difficult
Vocal cords			
Position	Abducted	Intermediate	Closed
Movement	None	Moving	Closing
Reaction to insertion of tracheal tube and/or cuff inflation			
Movement of limbs	None	Slight	Vigorous
Coughing	None	Diaphragm	Sustained (>10 s)

a. Intubation conditions
Excellent: All qualities excellent
Good: All qualities are either excellent or good
Poor: The presence of a single quality listed under "poor"

b. Laryngoscopy
Easy: Jaw relaxed, no resistance to blade in the course of laryngoscopy
Fair: Jaw not fully relaxed, slight resistance to blade
Difficult: Poor jaw relaxation, active resistance of the patient to laryngoscopy

In addition, a second blinded observer (observer 2) looked for evidence of diaphragmatic response to tracheal intubation. After confirmation of correct placement of tracheal tube using end-tidal capnograph, controlled ventilation was commenced using oxygen and nitrous oxide in the ratio 33:66 and halothane at an inspired concentration of 0.8 to 1.2% using a semi closed circle absorber system. Further management of the patient was handed over to the anaesthesia team in charge of the patient.

Postoperative day

Patients were interviewed by a nonblinded investigator on the morning following surgery and the following four questions were asked:

1. Did you feel weak or did you 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?
4. If you were to have an operation in the future, would you choose to be put to sleep in the same manner?

Statistical Methods

Three statistical methods were employed in this study: Chi-square analysis for gender distribution, assessment of cough and intubating conditions, Mann-Whitney U test for time to onset of clinical weakness, time taken to intubate, time interval between administration of relaxant and completion of intubation and time to loss of train-of-four response and Kruskal-Wallis test for age and weight distribution.

Results

The age, weight and gender distribution of the 60 patients studied are shown in *Table 2*. There was no difference in the age, weight or gender distribution between the groups.

Table 2: Demographic data

Group	Roc 0.6 (n=20)	Roc 1.0 (n=20)	SCh 2.0 (n=20)	Statistical significance
Age (years) Mean (SD)	33.85 (12.02)	31.25 (10.27)	39.40 (13.18)	P = 0.112*
Weight (kg) Mean (SD)	56.00 (10.08)	53.90 (9.78)	59.35 (10.03)	P = 0.113*
Gender (Male/ Female)	9/ 11	9/ 11	14/ 6	P > 0.2$

NS = Not significant * Kruskal-Wallis test $ Chi-square test

The mean time to onset of clinical weakness was 18.2± 2.19 seconds and 17.15± 1.84 seconds in the Roc 0.6 and Roc 1.0 groups respectively (*Table 3*). Increasing the dose of rocuronium brought about clinical weakness earlier but the difference was not statistically significant.

Intergroup comparisons were made with regard to pattern of muscle paralysis between the two doses of rocuronium. The incidence of impairment of cough and weak cough was observed in 40% and 30% in the groups Roc 0.6 and Roc 1.0 respectively (*Table 3*). One patient in the Roc 1.0 had an absent cough (*Table 3*). When the weak and absent cough were taken together as a single outcome, eight out of twenty patients in the Roc 0.6 group and 7 out of 20 in the Roc 1.0 group had a weak/absent cough. There was no significant difference between the two groups with regard to impairment of cough.

The train-of-four counts were recorded at the time of intubation as shown in *Table 3*. Rocuronium failed

to produce an acceptable level of neuromuscular blockade on adductor pollicis stimulation in 14 and 9 patients in Roc 0.6 and Roc 1.0 groups respectively. The time to loss of train-of-four response was shorter (84.0 ± 21.68 s) in the Roc 1.0 group compared to Roc 0.6 group (99.0 ± 30.38 s) but there was no statistically significant difference between the 2 groups (*Table 3*).

Table 3: Comparison of pattern of muscle paralysis between the two doses of rocuronium

Parameter	Roc 0.6 (n = 20)	Roc 1.0 (n = 20)	Statistical Significance
Time to onset of clinical weakness (s) Mean (SD)	18.2 (2.19)	17.15 (1.84)	P = 0.065@
Incidence of cough			
Normal	12 (60%)	13 (65%)	P > 0.2*
Weak	8 (40%)	6 (30%)	
Absent	0 (0%)	1 (5%)	
TOF count at time of intubation			
0/4	3	4	
1/4	1	4	
2/4	2	3	
3/4	3	3	
4/4	11	6	
Time to loss of train-of-four response (s) Mean (SD)	99.0 (30.38)	84.0 (21.68)	P = 0.115@

@ Mann-Whitney U-test *Chi-Square test

Intubating conditions were compared between the three groups (*Table 4*). When compared with the Roc 0.6 group, intubating conditions were similar in Sch 2.0 group but compared to both these groups where 14 patients had excellent intubating conditions, excellent intubating conditions were achieved in only 11 patients in group ROC 1.0. Increasing the dose of rocuronium did not improve the intubating conditions. The mean time taken to intubate i.e., the time from start of laryngoscopy to inflation of the cuff of the endotracheal tube after intubation was calculated and recorded in all the 3 groups (*Table 4*). The time taken to intubate was similar in all the groups. Intergroup comparisons were made with regard to the time interval between the administration of relaxant and the completion of intubation (*Table 4*). Compared to Roc 0.6 and Roc 1.0 groups which had similar times, the time interval was significantly short in the SCh 2.0 group (p = 0.001).

Table 4: Comparison of intubation characteristics

Parameter	Roc 0.6 (n= 20)	Roc 1.0 (n= 20)	SCh 2.0 (n= 20)	P value
Intubating conditions				
Excellent	14	11	14	P > 0.2*
Good	6	9	6	
Poor	0	0	0	
Time taken to intubate (seconds) Mean (SD)	16.1 (3.77)	15.95 (3.81)	15.7 (2.36)	P > 0.05@
Time interval between administration of relaxant and completion of intubation (s) Mean (SD)	97.75 (6.77)	94.45 (4.60)	77.60 (3.35)	P = 0.098@

*Chi-Square test @ Mann-Whitney U-test

All patients were satisfied with the induction technique used in this study and none of the patients complained of any discomfort or shortness of breath.

Discussion

Whenever a rapid sequence induction of anaesthesia is indicated in patients in whom succinylcholine is contraindicated, rocuronium administered using the timing principle as recommended by Seiber *et al* and Nelson *et al*, times the onset of peak neuromuscular blockade with the onset of anaesthesia and provides excellent intubating conditions for tracheal intubation almost as rapidly as succinylcholine.[6,7]

The objective of the 'timing' principle is to facilitate early tracheal intubation by administering the muscle relaxant before the intravenous induction agent and to administer the induction agent as soon as the first signs of clinical muscle weakness appear, so that the peak effect of the intravenous induction agent and that of the muscle relaxant may coincide more closely.

We studied the intubating conditions 60 seconds after administration of thiopentone sodium following intravenous rocuronium bromide using the timing principle in 40 patients allocated to 2 groups, namely group Roc 0.6 (rocuronium 0.6 mg/kg) and group Roc 1.0 (rocuronium 1.0 mg/kg). The intubating conditions were compared with intravenous succinylcholine hydrochloride at 2.0 mg/kg (group SCh 2.0). The results in groups Roc 0.6 and Roc 1.0 indicate that use of the timing principle enabled

tracheal intubation at 60 seconds producing good or excellent conditions for tracheal intubation, and it also shows that increasing the dose of rocuronium from 0.6 mg/kg to 1.0 mg/kg did not further improve the intubating conditions. Rocuronium 0.6 mg/kg produces intubating conditions comparable to succinylcholine 2 mg/kg. It should however be noted that Seiber *et al*, [6] evaluated intubating conditions at 45 and 60 seconds after administration of intravenous induction agent and the mean onset time to clinical weakness was 32 ± 4.9 seconds and 32 ± 5.3 seconds respectively which is much longer than 18.2 ± 2.19 and 17.15 ± 1.84 s in the Roc 0.6 and Roc 1.0 groups in our study. Our results are similar to that of Nelson *et al*, [7] who allowed a 20 second delay between the administration of rocuronium and thiopentone sodium.

We would agree with the recommendation by earlier workers that the 'timing' principle with rocuronium is a useful alternative when succinylcholine is contraindicated. However, we do not agree that it is a safe technique as concluded by Koh and Chen after their study on atracurium administered by the timing principle,[8] and the study by Silverman et al,[9] on vecuronium by timing principle because of a high incidence of impairment of cough as observed in our study.

We also studied the train-of-four count at the time of intubation and the time to loss of train-of-four response. The results revealed that there is no correlation between the onset time of muscle relaxation at the adductor pollicis and the intubating conditions, i.e., the onset time at the laryngeal adductors and the diaphragm occur earlier than that seen at the adductor pollicis as suggested by Donati et al.[10]

The time interval between the administration of relaxant and the completion of intubation was significantly shorter in the succinylcholine group compared to the other two groups which is because of the addition of the time to onset of clinical weakness to the 60 seconds after administration of thiopentone in both the rocuronium groups. However this time to onset of clinical weakness is also associated with risk of aspiration in a significant number of patients in both the groups.

All patients were satisfied with the induction technique used in our study and none of the patients complained of any discomfort or shortness of breath.

Conclusions

Employment of timing principle with rocuronium 0.6 mg/kg produces intubating conditions comparable to succinylcholine 2.0 mg/kg. Increasing the dose of rocuronium to 1.0 mg/kg does not provide better intubating conditions. Use of timing principle affects cough in a clinically significant number of patients.

Thus, when a rapid onset of neuromuscular blockade is desired in a clinical situation where succinylcholine is contraindicated, rocuronium administered using the "timing principle" seems to be a suitable alternative. However, in a situation where there is a high risk of aspiration of gastric contents, use of the "timing principle" with rocuronium might not prove to be an ideal technique.

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