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A COMPARATIVE STUDY TO EVALUATE THE EFFECTIVENESS OF TIMING PRINCIPLE AND PRIMING PRINCIPLE FOR TRACHEAL INTUBATION USING ROCURONIUM

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ABSTRACT

The present study is to compare the "Timing principle" and the "Priming principle" for tracheal intubation using rocuronium during balanced anesthesia by assessing the Intubating conditions and Hemodynamic changes during intubation. The succinylcholine is considered to be the best drug for rapid tracheal intubation because of its rapid onset and ultrashort duration of the action. The “priming technique” uses a sub-paralyzing dose of non-depolarizing muscle relaxant where 20% of ED 95 or 10% of the intubating dose was administered 2 to 4 min before administering an intubating dose. This technique has been proved to accelerate the onset of action by 30 to 60 seconds(5). In “timing principle” a single bolus of non-depolarizing muscle relaxant was given followed by the administration of the induction agent after the first sign of the onset of clinical weakness. The “high – dose regimen” was used when tracheal intubation has to be accomplished in less than 60 – 90 seconds(6). The study was conducted in Madras Medical College, Chennai The groups were comparable based on age and weight. Males were more in Group RP. Using the “Timing principle” with rocuronium 0.6 mg/kg consistently provides good to excellent intubating conditions at 60 seconds after the induction of anesthesia. Using the "Priming principle" with rocuronium 0.06 mg/kg followed by rocuronium 0.54 mg/kg consistently provides fair to good intubating conditions at 60 seconds after induction of anesthesia.

INTRODUCTION

The objective of the present study is to compare the "Timing principle" and the "Priming principle" for tracheal intubation using rocuronium during balanced anesthesia by assessing the Intubating conditions and Hemodynamic changes during intubation. The succinylcholine is considered to be the best drug for rapid tracheal intubation because of its rapid onset and ultrashort duration of the action. Although succinylcholine is widely used for tracheal intubation, its use is associated with malignant hyperthermia, hyperkalemia(1) in susceptible patients, myalgia, raised intraocular pressure and raised intracranial pressure(2, 3). Rocuronium was developed as an alternative to succinylcholine with the similar rapid onset and ultrashort duration of the action and with minimal side effects. The induction technique was modified to reduce the onset time(4). The “priming technique” uses a sub-paralyzing dose of non-depolarizing muscle relaxant where 20% of ED 95 or 10% of the intubating dose was administered 2 to 4 min before administering an intubating dose. This technique has been proved to accelerate the onset of action by 30 to 60 seconds(5). In “timing principle” a single bolus of non-depolarizing muscle relaxant was given followed by the administration of the induction agent after the first sign of the onset of clinical weakness. The “high – dose regimen” was used when tracheal intubation has to be accomplished in less than 60 – 90 seconds(6).

MATERIALS AND METHODS

The study was conducted in Madras Medical College, Chennai after obtaining ethical committee approval. Informed consent was obtained from all the patients preoperatively. We evaluated the intubating conditions with rocuronium bromide as the muscle relaxant according to the timing principle and compared it with the priming principle using Rocuronium bromide. We chose sixty patients undergoing elective surgical procedure. In the operating room, they were randomly allocated to two groups, Group RT (ROCURONIUM TIMING) and Group RP (ROCURONIUM PRIMING). Group RT received rocuronium bromide 0.6 mg/kg and was intubated 60 seconds after the onset of clinical weakness. (Timing principle). Group RP received a priming dose of rocuronium bromide 0.06 mg/kg. After 3 min, intubating dose of rocuronium 0. 54 mg/kg was given, and patients were intubated after 60 seconds. (Priming principle). We included only those in the age between 18-60 years with ASA I and II, MPC I and II, normal hematological and biochemical parameters. We excluded patients with

increased risk of pulmonary aspiration, neuromuscular disease, severe metabolic/electrolyte/acid-base disorders, known allergy to drugs. We also excluded patients on drug affecting neuromuscular function, pregnant patients, children, patients receiving any medication known to interact with a neuromuscular blocking agent.

All patients received Inj. Glycopyrrolate 5 µg/kg i. m. 45 min before induction as premedication. Inj. Fentanyl l 2 µg/kg i. v. was administered to the patient on the table. Patients were informed that they might feel weak before going to sleep during anesthesia. They were also informed about the post-operation questionnaire. Patients were monitored using pulse oximetry, ECG, ETCo2, and noninvasive blood pressure. All patients were pre-oxygenated for 3 min. GROUP RT: In the Timing principle group, patients were asked to keep their eyes widely open as long as possible. Inj. Lignocaine 1.5 mg/kg followed by Inj. Rocuronium 0.6 mg/kg was given. They were observed for the presence of pain on injection like withdrawal of hand. They were also closely observed for the first sign of clinical weakness, specifically the onset of ptosis. At this time, Inj. Thiopentone 5mg/kg was administered. 60 seconds after induction, tracheal intubation was performed by an experienced anesthesiologist who was unaware of the induction sequence. Intubating conditions were assessed according to the Cooper scoring scale.

GROUP RP: In the priming group, first a priming dose of Rocuronium 0. 06mg/kg was given. 3 min later, patients were induced with Inj. Thiopentone 5mg/kg, Inj. Rocuronium 0.54mg/kg and Inj. Lignocaine 1.5mg/kg. 60 seconds after induction, tracheal intubation was performed by an experienced anesthesiologist who was blindedto the induction sequence. Intubating conditions were assessed according to the Cooper scoring scale (Table 2).

Table 1: Demographic data

Parameters	Group RT (n=30)	Group RP (n=30)	p-value
Age	30.60±9.67	32.20±12.18	0.580
Male/Female	15/15	23/7	0.060
Weight	50.30±8.09	53.3±10.93	0.230

Table 2: COOPER SCORING SCALE

JAW RELAXATION	VOCAL CORD POSITION	RESPONSE TO INTUBATION	POINTS
Impossible	Closed	Severe coughing or bucking	O
Difficult	Closing	Mild coughing	1
Fair	Moving	Slight diaphragmatic movement	2
Easy	Open	No movement	3

On confirmation of correct placement of the tube, controlled positive pressure ventilation was instituted using nitrous oxide and oxygen. Intubation was scored as excellent (8-9), good (6-7), fair (fair), and poor (0-2). Pulse rate and blood pressure of all the patients were recorded from the time of administration of Inj. Fentanyl to and up to 5 min after intubation. Patients were also observed for any adverse effects like pain on injection, tachycardia, hypertension, bradycardia, hypotension, arrhythmia, laryngospasm, bronchospasm, anaphylactic/anaphylactoid reactions.

All the patients were interviewed 4-24 hours after the surgical procedure, and following questions were asked.

1. Did he/she feel weak immediately before going to sleep for your operation?
2. Did he/she feel short of breath immediately before going to sleep for your operation?

Statistical analysis: The differences in the proportions are tested for statistical significance using nonparametric Chi-square test for variables measured on a nominal scale. When testing for two factors, the Mann-Whitney "U" test or Wilcoxon two-sample test is used. For variables measured on a continuous scale, when testing for two groups, Student "t" test was used.

RESULTS

The groups were comparable based on age and weight. Males were more in Group RP.

The mean intubation time was 81.80±3.42 seconds in Group RT and 76.60±4.49 seconds in Group RP, the difference is statistically significant (p <0.001).

The Intubating conditions were assessed according to the Cooper scoring scale, and the results are tabulated in Table 3. The distribution of the number of cases by SCR-J (score - jaw relaxation) and the two groups was statistically significant (p=0. 009) with more proportion of cases in "score 2" among Group RP than Group RT. Moreover, Group RT has more no. of cases in score three than Group RP, which is statistically significant. The distribution of cases in score 1 and score three between Group RT and Group RP were found to be statistically insignificant. But the distribution of cases in score 2 (moving) found to be significant with more no. of cases in Group RP. The distribution of cases in score 1 and score three between Group RT and Group RP were found to be statistically insignificant. But the distribution of cases in score 2 (slight diaphragmatic movement) found to be statistically significant with more no. of cases in Group RP. The distribution of cases by SCR-Total scoring status categories and the two groups was observed to be statistically significant. Group RP has more number of cases in fair to good intubating conditions, while Group RT has more number of cases in good to excellent intubating conditions.

Table 3: intubating conditions

Scoring	Group RT (n=30)		Group RP (n=30)		p-value
	No.	%	No.	%	
SCR-Jaw relaxation					
Score 0: Nil	0	0. 0	0	0. 0	-
Score 1: Mild	0	0. 0	0	0. 0	-
Score 2: Moderate (Fair)	11	36. 7	22	73. 3	0. 050
Score 3: Good (Easy)	19	63. 3	8	26. 7	0. 040
SCR-Vocal cords					
Score 0: Closed	0	0. 0	0	0. 0	-
Score 1: Closing	0	0. 0	1	3. 3	NS

Score 2: Moving	2	6. 7	13	43. 6	0. 010
Score 3: Open	28	93. 3	16	53. 7	NS
SCR-Response to intubation					
Score 0:	0	0. 0	0	0. 0	-
Score 1: Mild coughing	0	0. 0	2	6. 7	NS
Score 2: Slight diaphragmatic movement	13	43. 3	19	63. 3	0. 040
Score 3: None	17	56. 7	9	30. 0	NS
SCR-T					
Scores 3-5: Fair	4	13.3	23	76. 7	<0.001
Score 6-7: Good	18	60	7	23	0.040
Scores 8-9: Excellent	8	26.7	0	0. 0	0.010

Cardiovascular parameters are given in Table 4. The mean systolic blood pressure values were lesser in Group RT than Group RP. The difference in the mean values of systolic blood pressure was observed to be not statistically significant between Group RT and Group RP at all the time points studied. The mean diastolic blood pressure values were lesser in Group RT than Group RP until two min after intubation and was either the same or higher after that. The difference in the mean values of diastolic blood pressure was observed to be not statistically significant between Group RT and Group RP at all the time points studied. The mean MAP values were lesser in Group RT than Group RP. The difference in the mean values of MAP was observed to be not statistically significant between Group RT and Group RP at all the time points studied. The mean pulse rate values were lesser in Group RT than Group RP at all time points measured. The difference in the mean values of pulse rate was observed to be not statistically significant between Group RT and Group RP at all the time points studied.

SpO2 was 100% in both the groups throughout the surgical procedure (before induction, at induction, at intubation, one min after intubation, two min after intubation, three min after intubation and five min after intubation).

There was no tachycardia in both the groups. Pain developed in 2 patients among Group RT and one patient among Group RP cases. Hypertension was encountered in 7 (23%) among Group RP and 5 (17%) among Group RT, the difference being statistically not significant (p=0.740). We encountered adverse effects in 8 (26.7%) among Group RP and 7 (23.3%) among Group RT, the difference is not statistically significant (p=0.770).

Table 4: Cardiovascular parameters

Time		Systolic blood pressure	Diastolic blood pressure	Mean Arterial pressure	Pulse rate
Before induction	**Group RT**	125. 10 ±10.54	84. 0±8.99	97. 20±7.31	83. 40±9.33
	Group RP	129. 60 ±10.81	87. 8±7.49	101. 80±8.63	85. 40±11.33
	p-value	0. 120	0. 060	0. 060	0. 460
At induction	**Group RT**	125. 10±10.54	84. 00±8.99	97. 60±8.70	87. 40±8.94
	Group RP	129. 80±12.74	88. 30±8.32	102. 20±9.90	89. 10±12.69
	p-value	0. 120	0. 060	0. 060	0. 560
At intubation	**Group RT**	131. 50±14.65	87. 70±10.64	102. 30±11.03	96. 00±8.40
	Group RP	138. 30±23.35	92. 90±14.66	108. 00±17.09	99. 80±19.79
	p-value	0. 180	0. 120	0. 130	0. 350
1 minute after int	**Group RT**	147. 70±15.21	98. 50±9.80	114. 70±11.02	100. 50±9.33
	Group RP	150. 00±13.68	102. 00±7.10	118. 00±8.56	106. 50±16.71
	p-value	0. 530	0. 120	0. 200	0. 100
2-mt after intubation	**Group RT**	133. 10±17.24	89. 20±12.30	104. 20±112.79	102. 90±11.78
	Group RP	136. 40±16.41	92. 20±10.35	106. 50±11.69	108. 70±14.37
	p-value	0. 460	0. 310	0. 480	0. 090
3-mt after intubation	**Group RT**	126. 70±13.47	87. 10±10.23	99. 60±11.89	100. 40±13.56
	Group RP	128. 10±14.00	85. 90±13.36	99. 70±12.68	104. 10±13.13
	p-value	0. 690	0. 700	0. 980	0. 290
5-mt after intubation	**Group RT**	122. 80±11.30	83. 60±10.24	96. 60±9.63	97. 90±14.11
	Group RP	121. 9±14.23	83. 50±10.83	96. 00±11.48	98. 10±12.81
	p-value	0. 770	0. 980	0. 850	0. 940

DISCUSSION

The cardinal requirements of General anesthesia are a loss of all sensation, sleep (unconsciousness), muscle relaxation and the abolition of reflexes. In the modern practice, these modalities are achieved by using a combination of drugs with each drug having a specific purpose.

In high-risk patients who are prone to aspiration, RSI is the preferred technique of induction. Succinylcholine continues to be the relaxant of choice as it consistently provides muscle relaxation within 60 to 90 sec and enables rapid tracheal intubation. Non-depolarizing muscle relaxants are used in RSI usually as pre-curarization. When succinylcholine is undesirable or

contraindicated, the onset of action of non-depolarizing neuromuscular blocking drugs can be accelerated by using high doses of an individual agent or by a combination of relaxants or by giving a priming dose of the relaxant before intubating dose. Recently, timing principle using non-depolarizing muscle relaxants have been used in RSI as it provides ideal intubating conditions within 60 – 90 sec. Silverman SM, Culling RD(7)demonstrated that the timing principle for RSI is a reliable alternative in cases where Succinylcholine is contraindicated. Mohamed Naguib(8) has shown that priming a rocuronium block with rocuronium resulted in a neuromuscular block similar to that of succinylcholine both in the onset of action and in intubating conditions. Musich J. Walts(9) demonstrated that pulmonary aspiration of gastric contents has been associated with a priming dose of vecuronium. This may be due to the rapid onset of the muscle relaxant at the adductor muscles of the larynx, as compared to the adductor pollicis. A similar potential risk may exist when the timing principle technique is used.

TIMING PRINCIPLE

Timing principle involves the administration of a single bolus dose of a non-depolarizing muscle relaxant in an adequately pre-medicated patient followed by the administration of the induction agent at the earliest sign of the onset of clinical weakness. The objective of the timing principle is to induce general anesthesia and muscle relaxation simultaneously rather than sequentially and also to reduce the effective onset time of the non-depolarizing muscle relaxant. Timing principle was introduced by Culling(6) in 1989. This technique has been applied to produce good intubating conditions rapidly with non-depolarizing muscle relaxants. In this technique, the time from the induction of anesthesia to complete relaxation is reduced, and the peak effects of the muscle relaxant and the intravenous induction agent may closely coincide. In the timing principle, the induction sequence is individualized on the onset of clinical weakness. Koyoma K, Katayama A et al.(10)in their study has demonstrated that excellent intubating conditions can be attained 70 seconds after thiopentone administration using timing principle with vecuronium. Koyoma k, Ishizuka et al(11) has shown that timing principle along with small priming doses of vecuronium is safe for rapid tracheal intubation.

TIME OF ONSET OF CLINICAL WEAKNESS

Thomas. J. Sieber et al.,(12) in their study using the timing principle with rocuronium used ptosis as the marker of earliest sign of clinical weakness as the neuromuscular block at the orbicularis oculi and the levatorpalpebraesuperioris are similar. Debaene et al.,(13) demonstrated that the onset of neuromuscular block in the diaphragm was faster than adductor pollicis but similar to orbicularis oculi. BeoitPlaud et al.,(14) in his study has stated that the corrugator supercilliaris and not the orbicularis oculi reflect the neuromuscular block at the laryngeal adductors. In our study, we used ptosis as the marker of earliest sign of clinical weakness.

Thomas. J. Sieber et al.,(12) used Inj. Midazolam and Inj. Fentanyl before induction. In our study, we used Inj. Fentanyl alone before induction of anesthesia as Inj. Midazolam can cause anterograde amnesia and find out if patients were satisfied with the technique postoperative would then be difficult to interpret. We wanted to assess the true extent of discomfort/satisfaction in our study.

In the postoperative questionnaire, only two patients in the Group RT and no patient in Group RP complained about weakness and shortness of breath before induction of anesthesia.

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, only two patients 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 post-op questionnaire) was not because of amnestic effects of anesthetics, but because the degree of muscle weakness present was not associated with discomfort. The restlessness was subjective as there was no evidence of desaturation while observing for the first sign of clinical weakness (ptosis).

PRIMING PRINCIPLE

Several groups of investigators have suggested giving a small sub-paralyzing dose of the non-depolarizer (about 20% of ED 95 or about 10% of the intubating dose) 2 to 4 min before administering a second larger dose for tracheal intubation. This procedure termed 'priming' has been shown to accelerate the onset of the block of most non-depolarizing neuromuscular blockers by about 30 to 60 seconds, with the result that intubation can be performed within approximately 90 seconds after the second dose. Rocuronium bromide and mivacurium chloride are non-depolarizing neuromuscular blocking agents that have been recently introduced to clinical practice. Rocuronium has a brief onset but an intermediate duration of action. Rocuronium may be the muscle relaxant of choice for Priming techniques because of it the rapid onset of action than the other non-depolarizing muscle relaxants. Griffith KE, Joshi GP, Whitman PF, Garg S demonstrated that priming with rocuronium 0.06mg/kg followed three min later by rocuronium 0.54mg/kg resulted in a neuromuscular block similar to that of Succinylcholine(15).

INTUBATING CONDITIONS

There are three methods to appropriately time the tracheal intubation: Clinical judgment, Neuromuscular monitoring either by twitch suppression (maximum blockade) or TOF ratio, or by fixed time after the administration of neuromuscular blocking agent such as 60 seconds, 90 seconds, 120 seconds, etc. The technique using judgment alone is relatively insensitive. S. Agoston(16) has demonstrated that meticulous recording of onset of neuromuscular block at adductor pollicis is probably obsolete. Use of single standardized qualitative rating scale for the assessment of intubating conditions is required to compare data from various studies. So we used scales that assess clinical criteria only to evaluate the quality of tracheal intubation.

Many factors influence the intubating conditions, the most important of which are the degree of relaxation of the muscle involved, the depth of anesthesia, the anatomy of the upper airways and the skill of the anesthetist. The superior intubating conditions due to succinylcholine is not only because of its rapid onset of action but also because of its greater potency at the laryngeal muscles than other nondepolarizing neuromuscular blocking drugs. However, Mohammed Naguib et al.,(8) have demonstrated that the priming

technique can be made to provide better intubating conditions for tracheal intubation in less than 90 seconds.

Intubating conditions were assessed in our study with the Cooper scoring scale which takes into consideration the ease of laryngoscopy, the position of the vocal cords during scope and the diaphragmatic response to tracheal intubation. Group RT and Group RP differed significantly on the intubating conditions. The intubating condition was fair in 13.3% and 76.7% in Group RT and Group RP, good in 60% and 23.3% in Group RT and Group RP respectively. The intubating condition was excellent in 26.7% of patients in Group RT. Twenty-two patients in Group RP had moderate (fair) jaw relaxation compared to eleven patients in Group RT. Thirteen patients in Group RP had vocal cords moving compared to two patients in Group RP. Nineteen patients in Group RP had slight diaphragmatic movement compared to thirteen patients in Group RT. This difference in the diaphragmatic movement was the reason for the discrepancy in the ratio of excellent to fair intubating conditions between Group RT and Group RP. In our study, we observed that the mean time for intubation using priming principle is 75s and resulted in fair (76.7%) to good (23.3%) intubating conditions. The average time for intubation using timing principle is 82 s and resulted in good (60%) to excellent (26.7%) intubating conditions.

I. Redai and S. A. Feldman(17) demonstrated that rocuronium is ineffective at priming rocuronium, and both rocuronium and vecuronium reduced the onset time of vecuronium block when given as priming agents. Rocuronium is an unusual drug in that its onset time is rapid compared to recovery time. Rapid onset time might be due to an early pre-synaptic site of action. An early pre-synaptic action would be of little effect in accelerating the onset of a drug already possessing this action, and this would explain its ineffectiveness at priming itself. This may be the reason for the fair to good intubating conditions using priming principle in our study.

HEMODYNAMIC CHANGES

Koyama K, Kawasaki et al.,(18) examined the circulatory response to intubation when timing principle was used with vecuronium. They concluded that the increase in blood pressure and the heart rate were significantly lower in the timing principle group than those in the succinylcholine group. They attributed it to the peak cerebral effect of thiopentone during intubation. I. Smith and R. S. G. Saad(19) shown that rocuronium was better than vecuronium for intubation but with no significant reduction in the hemodynamic response to intubation. In our study, there was no statistically significant difference in the hemodynamic parameters between the groups. The maximum mean systolic BP was 147.7 and 150.0 mmHg, maximum mean diastolic BP was 98.5 and 102.0 mmHg, maximum mean MAP was 114.7 and 118 mmHg, and maximum mean heart rate was 102.9 and 108.7 beats per minute for Group RT and Group RP respectively. The lack of significant difference might be due to the peak cerebral effect of the anesthetics at the time of intubation in timing principle.

INCIDENCE OF ADVERSE EFFECTS

There are reports of various adverse effects to rocuronium bromide. Pain on injection, hypotension, wheal response, flushing, bronchospasm, and anaphylaxis are possible after the administration of rocuronium. In the study conducted by Thomas. J. Sieber et al.,(20) 5 out of the 30 patients who received Inj. Rocuronium withdrew their forearm. But they did not conclude whether it was because of the pain on injection. K. F. Cheong and W. H. Wong (21) in their study found that lignocaine given before the administration of rocuronium reduced the incidence and severity of pain on injection of rocuronium. In our study, only two patients in Group RT and one patient in Group RP withdrew their forearm during injection of rocuronium. We hypothesize that these two patients might have withdrawn their forearm due to painful stimulus as all other patients had a prior administration of lignocaine. Hypertension was found in 5 patients in Group RT and seven patients in Group RP. Tachycardia was absent in both the groups. The incidence of adverse effects in both the groups is found to be statistically insignificant.

CONCLUSION

Using the “Timing principle” with rocuronium 0.6 mg/kg consistently provides good to excellent intubating conditions at 60 seconds after the induction of anesthesia. Using the "Priming principle" with rocuronium 0.06 mg/kg followed by rocuronium 0.54 mg/kg consistently provides fair to good intubating conditions at 60 seconds after induction of anesthesia. There are no significant alterations in the hemodynamic parameters during induction with rocuronium used as per the timing principle and the priming principle.

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