

Research Article**Effect of Ephedrine on Onset of Action of Rocuronium****Pradeep M S^{1*}, Hareesh S B²**¹Associate Professor, ²Assistant Professor, Department of Anaesthesiology, Institute of NephroUrology, Victoria Hospital Campus, Bangalore-560002, Karnataka, India***Corresponding author**

Dr. Pradeep M S

Email: pradeep.ms@gmail.com

Abstract: The purpose of this study is to assess the effects of ephedrine on onset time of rocuronium, by comparing onset time when using rocuronium alone and with priming with rocuronium. In this randomized clinical trial, 120 patients with the American Anesthesiologists Society (ASA) class I/II who required laryngoscopy and tracheal intubation for elective surgery were assigned to 4 groups. Priming dose of 0.04mg/kg rocuronium was given in group-P and group-PE. Inj. Ephedrine 0.2mg/kg I.V was given to group-E and group-PE. NPE group received no priming and no ephedrine. Patients were intubated after 30 seconds and intubating conditions graded according to the criteria of Cooper *et al.* Intubating conditions were clinically acceptable in all patients of the PE group compared to 2/28 of P, 2/29 of E, and 10/29 of the NPE groups ($p < 0.05$) vs. PE. The combination of ephedrine and propofol significantly improved clinical intubating conditions 30 seconds after priming with rocuronium, compared to priming without ephedrine, ephedrine without priming, and propofol alone.**Keywords:** Rocuronium, ASA, Ephedrine, Propofol

INTRODUCTION

Analgesia, hypnosis and muscle relaxation constitute the triad of requirements of general anesthesia to provide satisfactory operative conditions. Muscle relaxants are important adjuvant to assist in anesthetic practice.

With the advent of muscle relaxants, the patient needs just enough anesthetic to keep him unconscious and free from pain. Intubation is easier and atraumatic. Surgeries can be carried out in patients who were formerly thought unfit. For all these reasons, the combined use of general anesthesia and relaxants has been one of the greatest advances in anesthesia, since ether was introduced in 1846.

Anesthesiologists are in search of an ideal muscle relaxant which has cardiovascular stability, predictable distribution, elimination, drug metabolism and pharmacokinetics not affected by disease process.

Rocuronium, a non-depolarising muscle relaxant, has a rapid onset of time, an intermediate duration of action, rapid recovery characteristics coupled with cardiovascular stability, virtually no histamine release or other side effects.

This study has been undertaken to evaluate the efficacy of rocuronium, with particular reference to

onset of action, the effect of ephedrine on onset time of rocuronium, by comparing onset time when using rocuronium alone and with priming using rocuronium. Also the hemodynamic effects of rocuronium and ephedrine were studied.

A number of studies have been conducted on rocuronium properties since the first abstract published in 1988 relating to intubating conditions, priming dose pharmacokinetics, pharmacodynamics, haemodynamic properties [1-4]. Several studies have directly compared the intubating conditions, onset of action produced by rocuronium and suxamethonium and also with vecuronium [5].

Many authors in the past have discussed various ways of decreasing onset time of muscle relaxants, major work being the decreasing time for the muscle relaxants to reach the neuromuscular junction and also after priming. Few authors have also explained the haemodynamic effects of induction agents on the onset time of muscle relaxants [6].

MATERIALS AND METHODS**Study Design, Inclusion and Exclusion Criteria**

This prospective, randomized, double blinded and placebo controlled clinical study was conducted at Institute of Nephro-Urology, Bangalore, India between November 2013 to July 2014. The study protocol was

approved by the institutional research review and ethical committee. Inpatients posted to undergo elective surgeries under general anaesthesia requiring endotracheal intubation were chosen after taking informed consent from the patients.

Inclusion criteria were patients aged between 20 to 50 years with ASA (American Society of Anesthesiologists) class I and II. The exclusion criteria were those with anticipated difficult airway, laryngoscopic view > grade II, hypertension, diabetes, who were on medications known to interact with rocuronium or ephedrine, obese (BMI > 30), who were undergoing emergency surgery.

Randomization and study protocol

A total of 120 patients were randomly allocated into 4 groups with a minimum of 28 in each group. The groups were divided as: No priming no Ephedrine (NPE group); Priming with ephedrine (PE group); Priming alone (P group); Ephedrine alone (E group).

In the operating room, an I.V. line was established and ringer lactate solution started. Patients were continuously monitored with ECG, pulse oximetry, capnography, NIBP every minute throughout the procedure. All the patients were pre-oxygenated for 5 minutes. Inj. glycopyrolate 0.2mg I.V. was given followed by Inj. Fentanyl 2µg/kg I.V. Priming dose of 0.04mg/kg rocuronium was given in group-P and group-PE. Sham priming with normal saline was given in group-E and group-NPE. At the 3rd minute, Inj. Ephedrine 0.2mg/kg I.V was given to group-E and group-PE and sham ephedrine with normal saline was given to group-NPE and group-P. Induction was with Inj. Propofol 2mg/kg I.V over 20 seconds. This was followed by the intubating dose of rocuronium 0.4 mg/kg to group P and PE and 0.44mg/kg to groups NPE and E. Patients were intubated after 30 seconds and intubating conditions graded according to the criteria of Cooper *et al*[18].

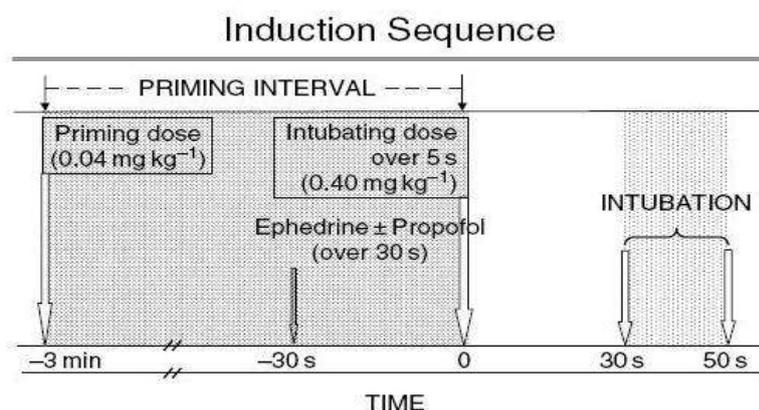


Fig. 1: Timeline describing induction in the priming groups.

Data Collection Techniques

Tracheal intubation was performed and assessed by an anesthesiologist with at least 8 years of clinical experience who was blinded to the group

allocation and not involved in the protocol. Intubating conditions were graded according to the criteria of Cooper *et al.* [18].

Table 1: Scoring of Intubation Condition (Cooper et al)

Score	Jaw Relaxation	Vocal Cord Position	Response to intubation
0	Poor	Closed	Coughing and bucking
1	Minimal	Closing	Mild coughing
2	Moderate	Moving	Light diaphragmatic movement
3	Complete	Open	None
Excellent = 8-9 Good = 6-7 Poor = 5-6 Bad = 0-4			

Excellent and good conditions were considered clinically acceptable. Haemodynamic variables like pulse rate, blood pressure, oxygen saturation, respiratory rate, EtCO₂ were noted every minute upto 10 minutes, from the time priming dose was given.

Statistical Analysis

The sample size was determined based on a power analysis and it was calculated that 28 was the minimum number required. Age was compared between groups using an unpaired t-test. The other data was

analyzed statistically using SPSS ver. 15 software. Paired and unpaired t test was used to evaluate continuous variables.

Chi square test and Fischer exact test were used to compare categorical variables. p value of <0.05 with two tailed significance was considered significant.

RESULTS

All four groups studied (n¼28-32) were comparable with respect to age, weight, height and sex ratio (Table 2).

All patients in all groups were intubated 30 seconds after the intubating dose of rocuronium within a 20 sec interval.

Intubating conditions (IC) (Fig. 2) were clinically acceptable in all patients of the PE group compared to 2/28 of P, 2/29 of E, and 10/29 of the NPE groups (p<0.05) vs. PE. Among the P, E and NPE groups the differences were not statistically significant except between groups P and E (p=0.863) (Table 3).

Vocal cord position score (VC) (Fig. 3) during intubation did not present statistically significant differences among the studied groups except between PE and NPE (p=0.005) with 27 patients of PE having complete opening of vocal cords versus only 15 of NPE group (Table 3).

Response to intubation (RI) (Fig. 4) was also significantly different only between PE group and NPE group (p=0.000) but not between other groups (Table 3).

Jaw relaxation (JR) score during intubation was good in 21 patients and moderate in 11 patients in group PE. Significantly better jaw relaxation was observed in the PE group compared to the P group and NPE group but not when compared to E group (p=0.013). Differences between the P, E, and NPE groups were not statistically significant (Table 3).

The baseline values of mean arterial pressure (MAP) and heart rate (HR) did not differ among the groups (Fig. 6, 7).

Mean arterial pressure was significantly increased in all groups after 3rd min (immediately after intubation) except between PE and E, NPE and P (p>0.01). Heart rate increased significantly in the P and E groups during the 9th min and between PE and NPE groups. There was no significant change in heart rate during the remaining times between groups.

During the priming interval no signs of patient discomfort, palpebral ptosis, blurred vision, respiratory difficulty or hypoxia were observed or reported. No patient had any arrhythmias during the study period.

Table 2: Demographic details

		Groups				Total
		Group NPE	Group PE	Group P	Group E	
Sex	M	11	17	10	17	55
	F	18	15	18	14	65
Total		29	32	28	31	120

Table 3: Statistical analysis of intubating conditions

		PE	NPE	p	PE	P	p	PE	E	p	NPE	P	p	NPE	E	p	P	E	p
		JR	Poor	0	0	0.000	0	0	0.007	0	0	0.013	0	0	0.021	0	0	0.029	0
Minimal	0		6	0	1		0	3		6	1		6	3		1	3		
Moderate	11		19	11	18		11	16		19	18		19	16		18	16		
Good	21		4	21	9		21	12		4	9		4	12		9	12		
VC	Closed	0	0	0.005	0	0	0.081	0	0	0.702	0	0	0.012	0	0	0.014	0	0	0.885
	Closing	0	1		0	0		0	0		1	0		1	0		0	0	
	Moving	5	13		5	5		5	6		13	5		13	6		5	6	
	Open	27	15		27	23		27	25		15	23		15	25		23	25	
RI	Bucking	0	1	0.000	0	1	0.022	0	1	0.022	1	1	0.070	1	1	0.060	1	1	0.971
	Coughing	3	12		3	5		3	6		12	5		12	6		5	6	
	Diaphragm	15	14		15	17		15	18		14	17		14	18		17	18	
	None	14	2		14	5		14	6		2	5		2	6		5	6	
IC	Bad	19	3	0.000	19	9	0.017	19	9	0.008	3	9	0.004	3	9	0.004	9	9	0.872
	Poor	13	16		13	17		13	20		16	17		16	20		17	20	
	Good	0	10		0	2		0	2		0	2		0	2		0	2	
	Excellent	0	0		0	0		0	0		0	0		0	0		0	0	
CA	Acceptable	32	19	0.000*	32	26	0.001*	32	29	0.003*	19	26	0.000*	19	29	0.000*	26	29	0.863*
	Non acceptable	0	10		0	2		0	2		10	2		10	2		2	2	

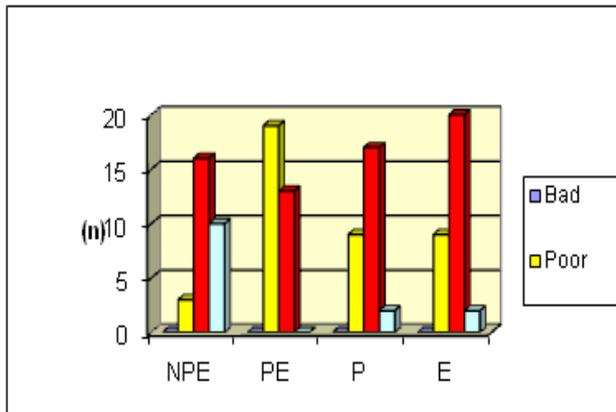


Fig. 2: Intubating conditions

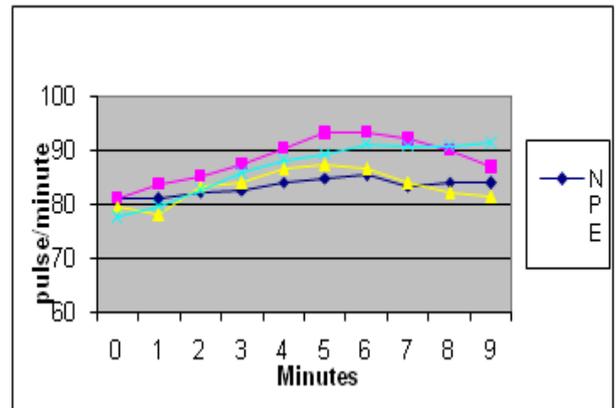


Fig. 6: Comparison of Mean Pulse Rate

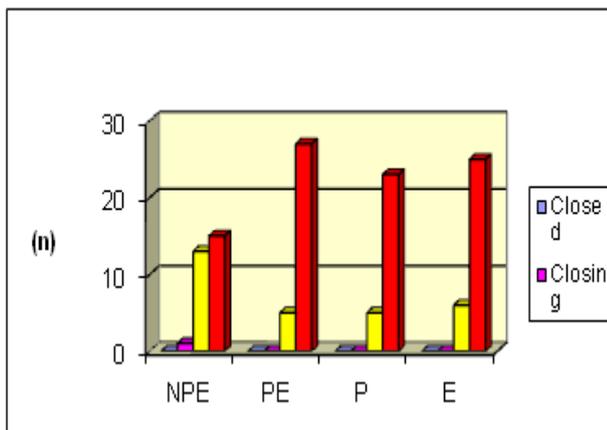


Fig. 3: Vocal cord position

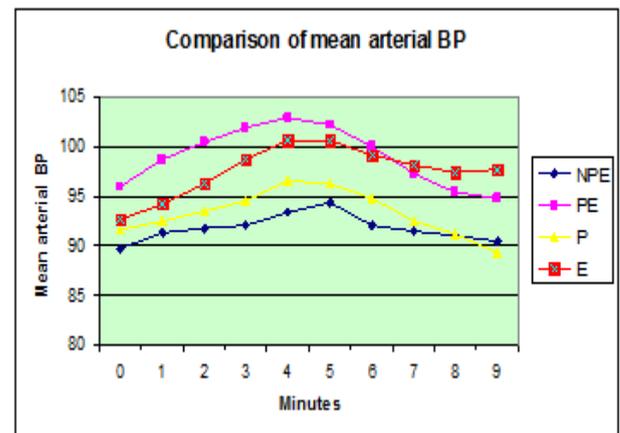


Fig. 7: Comparison of Mean Arterial BP

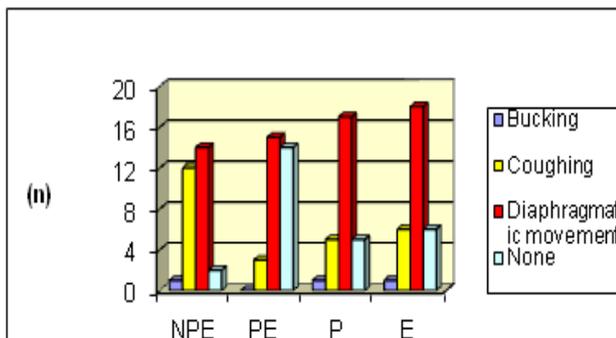


Fig. 4: Response to Intubation

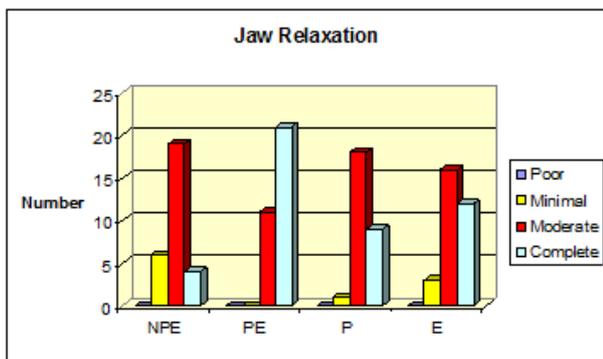


Fig. 5: Jaw Relaxation

DISCUSSION

The main finding of this study is that the combination of ephedrine and propofol significantly improved clinical intubating conditions 30 seconds after priming with rocuronium, compared to priming without ephedrine, ephedrine without priming, and propofol alone. Priming consisted of a subparalyzing dose of 0.04mg/kg of rocuronium, followed 3min later by an intubating dose of 0.4mg/kg. No signs of muscular weakness or evidence of respiratory difficulty were either appreciated or reported of clinical relevance.

The rationale of the divided dose technique of administration of non-depolarizing muscle relaxants for facilitation of rapid tracheal intubation is based on the high margin of safety of neuromuscular transmission, allowing 70-75% occupancy of the cholinergic receptors without any significant effect on neuromuscular activity. The priming principle relies on the assumption that the administration of a second larger dose of a muscle relaxant, at the time of peak effect of the priming dose, will rapidly increase receptor occupancy to the 90-92% level required for a profound neuromuscular block [4]. However during the relatively long priming interval, the awake patient may suffer from distressing symptoms of muscle weakness like blurred vision, dysphagia and respiratory embarrassment. The size of the priming dose, the

intubating dose, as well as the priming interval, are therefore crucial in the efficacy of the priming technique and in the reduction of the incidence of possible side-effects [7].

Munoz *et al.* in particular studied the effect of vasopressor ephedrine on the onset time of Rocuronium [8], followed by Peter Szmuk *et al.* [9] and others.

Priming with rocuronium resulting in a reduction of onset time has been successfully investigated in several studies. Naguib *et al.* demonstrated that 0.06mg/kg of rocuronium (20% ED95) followed 3 min later by 0.54mg/kg reduces the onset time by approximately 20-35%, compared to a single intubation dose of 0.6mg/kg of rocuronium [10].

The onset time of muscle relaxants depends on the rate at which a pharmacologically effective concentration is achieved in the biophase, that is to say the neuromuscular cleft. In turn, this rate is influenced by several factors, such as the potency of the drug, the dose administered, and the cardiovascular status, namely cardiac output and muscle blood flow. Moreover, the onset time of drugs with rapid onset, such as rocuronium, chiefly depends on the circulation time to the muscle, whereas the process of redistribution of the drug from an extrajunctional to a junctional area is a more important determinant for the onset of action of vecuronium and mivacurium [3]. Ephedrine, which produces an increase in both cardiac output and muscle blood flow, reduces the onset time of rocuronium, but not that of vecuronium [11]. However, this has been challenged in further studies demonstrating that ephedrine improves intubating conditions when using vecuronium also.

Ephedrine in doses of 70, 140, 210, and 260 µg/ kg has been proven effective in the prevention of hypotension following induction with propofol [6, 12].

The rationale for combining the priming principle with ephedrine comprises partial occupancy of the cholinergic receptors by the priming dose and acceleration by ephedrine of the residual receptor occupancy once the intubating dose of the neuromuscular blocker has been administered, hence further reducing the time for clinically acceptable intubating conditions.

Since it has been suggested that ephedrine improves intubating conditions by promoting a faster delivery of NMBAs to their site of action, haemodynamic measurements should be performed prior to attempting intubation. In contrast our measurements were performed at baseline and after intubation because of the short interval between the intubating dose and laryngoscopy. Ezri *et al.* demonstrated an increase in cardiac output (measured using NICO monitor), following the administration of

ephedrine, but only after intubation was performed and intermittently every 3min, thus not accounting for subtle changes immediately prior to intubation [13]. The validation of the haemodynamic hypothesis of action of ephedrine should require measurements of cardiac output and muscle blood flow between the induction of anaesthesia and laryngoscopy.

We selected a dose of 200 µg/ kg of ephedrine because this dose was shown to prevent the hypotensive response to anaesthetic induction with propofol without causing any clinically significant overshoot in either systolic or diastolic pressure. However, in our study, and as previously observed by Tan *et al.*, the combination of ephedrine and propofol caused a statistically significant increase in MAP, though not in heart rate and therefore caution should be exercised in the use of this combination in patients with ischaemic heart disease [12]. On the other hand, the use of the combination of propofol and ephedrine is theoretically safer for haemodynamically unstable patients. Further studies may be needed to identify the ideal dose of ephedrine for this combination.

The present trial evaluated only the clinical intubation conditions without monitoring the degree of neuromuscular blockade. With the exception of Tan *et al.* [12], the effect of ephedrine has been previously measured as a reduction of onset time at the adductor pollicis. Conversely, in the present study the primary variable was clinical intubating condition at a fixed time. Further studies may be needed to quantify the onset of neuromuscular blockade when combining priming with ephedrine. However, Kopman *et al.* demonstrated that excellent intubating conditions, 75 s after 0.5mg/ kg of rocuronium, did not correspond to comparable effects on twitch response measured at the adductor pollicis [14]. Such results are in accordance with that initially stated by Agoston and subsequently advised by the Copenhagen International Consensus Conference on Good Clinical Research Practice [15,16]. 'Intubation conditions and paralysis of the adductor pollicis muscle may be poorly correlated and complete paralysis of this muscle may be a poor indicator of intubation time or of the time to evaluate intubation conditions'.

In a theoretical analysis of safety and timing of the priming dose, Kopman *et al.* concluded that a dose equivalent to 10% of ED95 will rarely produce a measurable neuromuscular effect [14].

Indeed, the adverse effects reported involved higher priming doses. However, in several studies on rocuronium in which the priming dose ranged between 0.06 and 0.1mg/ kg (20-33% of ED95) no adverse effects were reported during the priming interval [17]. In the present investigation we selected a priming dose of little more than 10% of ED95, which probably

accounted for the absence of both subjective and clinical adverse effects during the priming interval.

CONCLUSION

The combination of ephedrine and propofol had significantly improved the clinical intubating conditions 30 seconds after priming with rocuronium, compared to priming without ephedrine, ephedrine without priming, and propofol alone.

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