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A Controlled, Double Blind, Prospective Study of Onset of Muscle Relaxation with Rocuronium with or without Pretreatment with Ephedrine.

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ABSTRACT

This prospective, double blind, controlled study compared the speed of onset of rocuronium with or without ephedrine. Patients aged 18-60 years, ASA grade I or II, posted for surgical procedures were allocated after a priming dose of rocuronium to either receive ephedrine (210 mcg/kg) (RE) or saline (RS) before intubation. Train of four (TOF) was checked after administration of rocuronium and time required for the disappearance of all four twitches was ascertained. Clinical parameters, time for laryngoscopy and intubating conditions were judged by blinded anaesthetists using the Cooper's score. Mean (SD) time for the complete relaxation, time for laryngoscopy and intubating conditions (Cooper's score) were not found to be statistically significant between RE and RS group. The Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Heart Rate (HR) were significantly higher in the RE group as compared to the RS group. Our results indicate that the benefits of using ephedrine at a dosage of 210 mcg/kg before rocuronium are not significant as compared to placebo and hence does not support the use of ephedrine before propofol-rocuronium to improve the onset of rocuronium.

KEYWORDS RSI, rocuronium, ephedrine with rocuronium.

INTRODUCTION

Succinylcholine is still the drug of choice for Rapid sequence intubation (RSI), as highlighted by the Cochrane review (2008) as compared to rocuronium.1 The depolarising agent succinylcholine is considered to be a clinically superior drug as it has a shorter duration of action and provides better intubating conditions.1 Succinylcholine, however, is associated with serious adverse effects. Among the many replacements that has been tried, in order to avoid the adverse effects of succinylcholine, rocuronium is probably the most popular one.

Rocuronium, a nondepolarising agent has been attempted as a replacement for succinylcholine, for RSI, owing to its faster onset of action.1 To improve the dose response of rocuronium, various adjuvants/ pretreatment drugs have been tried to modify the onset of action. Among the drugs attempted, ephedrine, phenylephrine and sodium bicarbonate are the most popular ones.2,3,4 Ephedrine at various dosages ranging from 30 – 210 mcg/kg/min, before rocuronium has been attempted with mixed results.5 Ephedrine, in most studies, is found to prevent the drop in blood pressure secondary to administration of induction agent.6,7 Sodium Bicarbonate is found to be beneficial, where as phenylephrine is found to have negative effects with rocuronium. Priming technique is also found to be useful in improving the dose-response of rocuronium.8

The main aim of our study was to ascertain the effect of ephedrine on the speed of onset of action of Rocuronium with propofol induction. We hypothesized that, Ephedrine used before the administration of the induction agent, should improve the hemodynamics to deliver rocuronium faster onto the neuromuscular junction. We combined priming technique to further improve the speed of onset as shown by previous studies. We compared the onset of relaxation at adductor pollicis and intubating conditions using Cooper's score.9

METHODS

After taking approval from the institutional ethics committee, written informed valid consent was taken from all patients after explaining the study protocol.We enrolled 100 patients aged 18-60 years, ASA grade I/II, presenting for elective and emergency surgical procedures under general anaesthesia. Patients were randomised into two groups: Rocuronium with ephedrine (RE) and rocuronium with saline (RS). The group allocation was done using an approved method, where every successive patient was assigned a number from 1- 100, such that every odd numbered patient was allocated as the study (RE) group and every even numbered patient was assigned as a control group (RS).10

Patients with neuromuscular, hepatic, renal diseases, abnormal airway anatomy (Mallampati score 3 and 4), pregnancy, medication that may interfere with neuromuscular blockade, or patients with a known allergy to opioids, neuromuscular blocking drugs, or other medications used in general anaesthesia were excluded from the study.

Pre-anaesthetic assessment included medical/surgical history, general/systemic examination, airway examination and routine investigations, such as complete haemogram, urea- electrolytes and urine routine. Liver function tests, chest x-ray and electrocardiogram were considered where indicated. The premedication was given 10 min prior to transfer to operating theatre, which included Inj Ranitidine 1mg/kg IV and Inj Metoclopramide 0.2mg/kg IV. In the operation theatre, cardioscope, pulse oximeter and noninvasive blood pressure were attached and the baseline parameters were noted.

Inj Fentanyl 2mcg/kg IV was administered followed by priming dose of rocuronium 0.06 mg/kg in all the patients. After 3 minutes of preoxygenation, pretreatment dose of ephedrine 210 mcg/kg or saline followed by induction dose of propofol 2 mg/kg after 30 seconds was administered. After confirming loss of conciousness, supramaximal current strength was determined by stimulating ulnar nerve at the wrist, using the peripheral nerve stimulator (PNS) (Innervator 25.2). The contraction of adductor pollicis (visual and tactile) was used to determine the supramaximal stimulus, by serially increasing the current strength starting from 10 milliAmps upwards, till no more increase in the current strength was noted. Inj rocuronium 0.6 mg/kg was administered followed by ventilation with oxygen –nitrous oxide (50 – 50%) in all the patients. Train of four (TOF) at the adductor pollicis at 2 Hz every 15 seconds

was monitored till the loss of all four responses to supramaximal stimulus. Inj esmolol 0.5 mg/kg IV was administered and patient was ventilated with 100% oxygen for one minute before laryngoscopy and intubation.

Time required for introduction of laryngoscope, intubation and withdrawal of laryngoscope after intubation was noted. Inj midazolam was administered 0.03 mg/kg after intubation. Anaesthesia was maintained with propofol infusion. Vital parameters were noted at every intervention or drug administration. Cooper's score was used to grade the intubating conditions.9 Cooper's Scale (score) 9 8 7 6 5 4 3 2 1

Scoring	0	1	2	3
I. Jaw relaxation	Poor	Minimal	moderate	good
II. Vocal–cord position	Closed	closing	moving	open
III. Intubation response	severe coughing	mild coughing	light diaphragmatic movement	none

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS software version 13. The qualitative variables (gender) were presented as frequency and percentage and compared between the two groups using chi-square test.

All quantitative variables namely, time for relaxation, time for laryngoscopy, Cooper's scores, blood pressure, heart rate were represented in terms of mean and standard deviation and compared using independent samples t test. Comparison was done at 5% level of significance.

RESULTS

Fifty patients each were recruited in the two groups . In the RE group, 16 (32%) were male; mean age was 41.04 years (± 9.15) and mean weight 49.8 kg (± 8.28). In the RS group, 23 (46%) were male; mean age was 49.80 years (± 8.28) and mean weight was 52.24 kg (±9.26). There were no important differences between patient characteristics between RE and RS, as shown in Table 1.

Table 1 about here.

Preoperative vital parameters of all patients were found within normal range. Mean baseline value of systolic blood pressure with standard deviation (SD) was 113.6 (6.6) mm of Hg vs. 115.8 (9.7) mm of Hg. Mean baseline pulse rate was 89.5 (14.7) per min vs. 91.2 (13.2) per min.

The rise in systolic as well as diastolic blood pressure was statistically significant in the study group after administration of ephedrine with a $p<0.001$.Comparison of pulse rate in study and control groups showed a significant rise in the pulse rate during the administration of ephedrine which lasted for up to 10 minutes following intubation, with $p<0.001$, as shown in Figure 1 and Figure 2.

Figure 1 about here.
Figure 2 about here.

The time for complete relaxation (loss of four responses of TOF) and time for laryngoscopy were 132.64 ±44.38 as compared to 136.12±39.98 seconds, 26.26 ±6.14 as compared to 28.12 ±7.04 seconds in RE and RS group respectively.The mean Cooper's score was 8.52±0.71in RE group and 8.36±0.72 in RS group respectively, as shown in Table 2. All the parameters were comparable and there was no significant difference found.

Table 2 about here.

There were incidences of diplopia in 3 patients, dizziness in 2 patients, dyspnoea in 1 patient after priming, in the RE group. There were 3 cases of diplopia, 1 case of dizziness after priming, and one incidence of damage to anterior pillar during intubation in the RS group.

DISCUSSION

Rocuronium is thought to be an appropriate replacement for depolarising agent, succinylcholine during Rapid Sequence Intubation. To improve the dose response of rocuronium, various pretreatment drugs like ephedrine , phenylephrine , sodium bicarbonate are being used.2,3,4 Priming technique is also found to be useful in improving the dose-response of rocuronium .8 We studied the effect of pretreatment of ephedrine on the speed of onset of action of Rocuronium with propofol induction.

The principal finding in our study was that the onset of action of rocuronium, was not significantly shortened compared to placebo, when pretreated with ephedrine (210 mcg/kg) before propofol-rocuronium induction. Ephedrine, in our study, was administered in the RE group 30 seconds before administration of Propofol. Several clinical studies have found improved onset time of rocuronium, when administered after ephedrine.11,12,13,14 This effect was hypothesized to be due to possible delivery of the relaxant to the neuromuscular junction at a faster rate, due to increased hemodynamics. Timing of ephedrine has been variable between investigators, with most administering before the induction agent 7 and some before the muscle relaxant2. Han W et al, conducted a study comparing administration of 70 micrograms of ephedrine, 30 seconds and 4 minutes before the administration of rocuronium. They found significant shortening in the onset of rocuronium in the 4 minutes group.2

Our study employed an ephedrine dosage of 210 mcg/kg in the RE group. The dosage of ephedrine that has been used ranges from 30 mcg/kg/min to 210 mcg/kg/min.5,9 Gopalkrishna MD et al have found beneficial effect of the ephedrine restricted to dosages below 70 mcg/kg/min. The authors have hypothesized the possible vasoconstrictive effect of ephedrine with higher dosages above 150 mcg/kg/min.5 In a clinical study, conducted on elective surgical patients by Komatsu et al15, ephedrine at a dosage of 210 µg/kg, one minute prior to vecuronium administration, failed to accelerate the onset time, as measured at adductor pollicis with the help of accelerometry. Herweling et al measured the effect of ephedrine (110 mcg/kg) on the cardiac output, by measuring muscle blood flow in pigs, where they compared Etomidate, Thiopentone, Ephedrine + thiopentone before rocuronium. The onset of action was measured at adductor pollicis with mechanomyography and they did not find statistically significant difference among the three groups.16 The results of these studies were similar to our study, where we failed to demonstrate any increased speed of onset, as measured by TOF at the adductor pollicis.

Madhusudan et al concluded that cases where suxamethonium is contraindicated, rocuronium with ephedrine pre-treatment may be used for intubation, though the quality of intubation is slightly poor but still clinically acceptable.17

Priming technique involves using 1/10th of the intubating dose of a nondepolarising agent prior to the administration of the intubating dose.6,18 It should not cause unpleasant symptoms, but should occupy a considerable portion of the postsynaptic nicotinic acetylcholine receptors and shorten the onset time after administration of the intubation dose. Schmidt et al have concluded that priming interval of 2-6 minutes should be safe and effective.18 In our study, the timing interval between priming and intubating dose of rocuronium has not been fixed as the intubating dose of rocuronium was administered after a variable time interval after the loss of conciousness with induction agent propofol.

Schimdt et al have compared the contractions at the laryngeal muscles and adductor pollicis, using laryngeal surface electrodes with recurrent laryngeal nerve stimulation and electromyography of the adductor pollicis with the left ulnar nerve stimulation, respectively.18 They have found that the mean time for paralysis of laryngeal adductor muscles significantly earlier (44.7 seconds) as compared to adductor pollicis

(105.4 seconds). The dosage of Ephedrine used, the timing of ephedrine, and the site of measurement of complete paralysis, could be the reason, that our study failed to demonstrate any significant improvement in the speed of onset of rocuronium.

Rocuronium has been tried in various dosages ranging from 0.45-1.2 mg/kg. Rocuronium at dosages of 1.0 – 1.2 mg/kg produces adequate conditions for intubation in 60-90 seconds.18 Cochrane review (2008) observed that, though succinylcholine was clinically superior due to shorter duration of action, no statistically significant differences were found between succinylcholine and rocuronium 1.2mg/kg, as regards to onset of action was concerned.1 However, we used a dosage of 0.6 mg/kg, to ascertain the effect of ephedrine as any improvement in the onset of action would be better demonstrated with a smaller dose of rocuronium, as compared to a larger dose of 1.2 mg/kg.

The increased haemodynamic response as a result of ephedrine, as noted in our pilot study was undesirable before intubation. Esmolol is a useful agent to control the heart rate before intubation. Use of esmolol before the administration of rocuronium significantly prolonged the onset of the blockade.14 In our study, we administered esmolol after the administration of rocuronium and after the complete paralysis of muscles, i.e. after the zero response on the peripheral nerve stimulator. Hence the administration of esmolol did not alter the onset of action of rocuronium in our study. Intubation was attempted after one minute as the peak action of esmolol is at one minute. Similar study was done with Cisatrcurium and was found to be effective.19 We counted the time required for laryngoscopy as a measure of ease of intubation. We measured the time interval from the insertion of laryngoscope to removal of laryngoscope. This method of calculating the duration of laryngoscopy was also used by Gopalkrishna et al.5

A lower dose of ephedrine (between 70 – 150 mcg/kg) administered 4 minutes before rocuronium and muscle relaxation measured at laryngeal muscles, would probably establish the role of ephedrine with rocuronium as an aid to rapid sequence intubation.

Table 1 Comparison of mean (SD) age, mean (SD) weight, and sex ratio between the RE and the RS groups. (n=50)

	RE	RS
Age (yrs)	41.04 ± 9.15	49.80 ±8.28
Weight (kg)	49.80 ±8.28	52.24 ±9.26
Sex (M/F)	16/34	23/27

Table 2 Comparison of mean (SD) Time for blockade, time for laryngoscopy and Cooper's score between the RE and the RS groups.

	RE	RS	p value
Time for blockade (sec)	132.64 ±44.38	136.12 ±39.98	0.681
Time for laryngoscopy (sec)	26.26 ± 6.14	28.12 ±7.04	0.163
Cooper's score	8.52 ± 0.71	8.36 ± 0.72	0.265

Figure 1 Comparison of Systolic blood pressure (SBP) and diastolic blood pressure (DBP) between RE group and the RS groups.

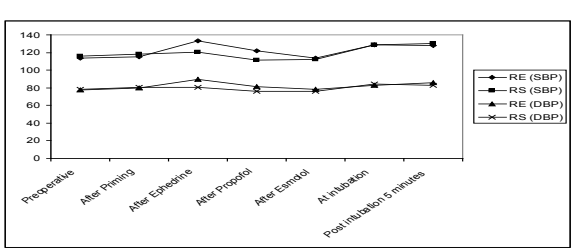
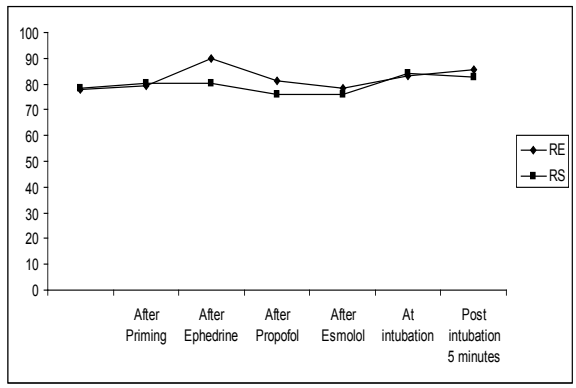


Figure 2 Comparison of heart rate between the RE and the RS group during various interventions.



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