

To Study The Effect of Pretreatment With Ephedrine on The Intubating Condition And Hemodynamic Characteristics on The Rocuronium In Patient Undergoing General Anaesthesia: A Randomised Controlled Study

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Abstract: Onset time of neuromuscular blocking drugs depends on the rate at which a pharmacologically effective concentration is achieved in the neuromuscular junctional cleft which in turn is determined by muscle blood flow and cardiac output. Ephedrine being a potent sympathomimetic can produce an increase cardiac output and muscle blood flow thereby increasing the onset time of rocuronium. The objective of the study was to study the effect of pretreatment with ephedrine on the intubating conditions and duration of effect and hemodynamic characteristics using rocuronium.

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I. Introduction

Succinylcholine, a short acting depolarizing muscle relaxant with rapid onset of action has numerous side effects, so there has been a continual search for a muscle relaxant that can replicate the onset time of succinylcholine. Rocuronium is being used as an alternative to succinylcholine for rapid sequence induction, however its dose dependent onset and duration of action occasionally limits its use. Since onset time of neuromuscular blocking drugs is determined by muscle blood flow and cardiac output^{1,2}, various studies^{3,4,5} using induction agents that maintain cardiac output and blood pressure have been done. Ephedrine, by increasing cardiac output and tissue perfusion, can result in a faster delivery of rocuronium to the laryngeal and diaphragmatic muscles and thus may shorten the onset of action of rocuronium and improve intubating conditions. Our primary objective was to study the effect of pretreatment with ephedrine 70 mcg/kg on the intubating conditions and duration of effect using propofol 2.5 mg/kg and rocuronium 0.6 mg/kg. Secondary objective was to study the haemodynamic characteristics at intubation and observe any untoward effect.

II. Material And Methods

After obtaining approval from the institutional ethical committee and informed consent from patients, 60 patients ASA I and age varying between 20-60 years, weighing 35-75 kg who were to undergo elective surgeries were included in the study. Patients were randomized into two groups using random allocation software and blind randomized study was done in which one of the co-guide prepared and delivered the drugs to the patient and maintained the record in computer. The second co-guide/guide performed the intubation and judged the intubating conditions, whereas recording of vitals and twitch response was done by the observer. The drugs given to the patient were disclosed at the end of the study.

Group I (E group): received propofol 2.5 mg/kg and 5ml normal saline with ephedrine (70 mcg/kg) and rocuronium 0.6 mg/kg, one minute after induction.

Group II (Control Group): received propofol 2.5 mg/kg and 5 ml of normal saline without ephedrine and rocuronium 0.6 mg/kg, one minute after induction.

Patients with anticipated difficult airway, pregnancy, morbidly obese patients, history of significant cardiac, respiratory, renal, hepatic or CNS disease, history of known allergy to drugs, neuromuscular disorders, hypertension and psychosis were excluded from the study.

A detailed history and thorough clinical examination was conducted and study protocol was explained to all the patients during preanaesthetic evaluation. The participants were made familiar to neuromuscular monitoring. Patients were shifted to operating room and monitors were attached. All patients were monitored with automated non-invasive blood pressure, pulse oximetry, ECG and neuromuscular monitor (TOF watch Organonoteknika B.V.). Without the knowledge of intubating anaesthetist (second anaesthetist), the first

anaesthetist (co-guide) prepared the drugs, to be given according to the groups assigned as per the random allocation computer generated software system. Baseline measurement of heart rate, blood pressure and SPO₂ were noted.

After preoxygenation for 3 minutes, anaesthesia was induced through an intravenous line with butorphenol 0.02 mg/kg, followed by one of the two groups mentioned above. Patients in E group received ephedrine 70 mcg/kg rounded off to the nearest 0.5 mg diluted to 5 ml with normal saline. Patients in control group received only normal saline 5 ml. After 1 minute, patients in both the groups were induced with intravenous propofol 2.5 mg/kg. One minute after propofol, patients in both the groups were given rocuronium 0.6 mg/kg over 5 seconds and mask ventilation continued with 100% oxygen. Neuromuscular monitoring was started after 20 seconds of rocuronium administration with single twitch of 0.1 Hz every 10 seconds with current adjusted to 50 mA, on the arm contralateral to intravenous line and response of adductor pollicis was noted.

Intubation was performed at neuromuscular block 90% or greater by the second anaesthetist who was blind to the study. Heart rate, blood pressure and temperature were monitored continuously and recorded a baseline, 1 minute after ephedrine dosing, 1 minute after induction, immediately after intubation and 1, 2, 3, 4, 5 and 10 minutes after intubation and thereafter every 10 minutes till the completion of surgery.

After laryngoscopy and intubation, the second anaesthetist performing the intubation was asked about the three different variables: jaw relaxation, vocal cords position and response to intubation. Assessment was based on the ease of laryngoscopy manifested by jaw relaxation, the position of vocal cords and the reaction to tracheal intubation and cuff inflation as described by Cooper et al.⁶ (1992). A total intubation score of 8-9 was considered excellent, 6-7 good, 3-5 poor and 0-2 bad.

Scoring of intubating conditions

S	JR	VCP	R
•	0 Poor (impossible)	Closed	Severe coughing(bucking)
•	1 Minimal (difficult)	Closing	Mild coughing
•	2 Moderate (fair)	Moving	Slight diaphragmatic movement
•	3 Good (easy)	Open	None

S= score, JR = Jaw relaxation, VCP = Vocal cord Position, R = response to intubation

After intubation, anaesthesia was maintained with 66% N₂O, 33% Oxygen and 0-1% Isoflurane. Rocuronium 0.1mg/kg was given as maintenance dose, when patient is out of anaesthesia, manifested by 25% of twitch response on TOFwatch. Patients were reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.2 mg/kg. Statistical significance of the results was done by using students 't' test with SPSS 16 statistical pack (p≤0.05 was considered significant).

III. Result

In the control group, mean ± SD age values of 43.43 ± 14.9 did not differ significantly from respective values of 37.87 ± 11.95 in the group receiving ephedrine. Similarly mean ± SD weight values of 53.6 ± 7.52 in the control group did not differ significantly from respective values of 56.23 ± 7.68 in the group receiving ephedrine. Gender difference was also not significant between two groups. Therefore the groups were comparable (p value > 0.05).

The values of baseline heart rate in the control group and the group receiving ephedrine were 74 ± 12.04 and 80.03 ± 12.13 respectively. There was no significant difference in the values of two groups (p value >0.05). However there was significant difference in the heart rate between two groups, one minute after the administration of the study drug i.e. ephedrine, as compared to control (normal saline) (table 1). The heart rate was 82.03 ± 12.19 in the ephedrine group, which was significantly higher than the control group, where it was 73.57 ± 11.33 (p value < 0.01).

Table 1. Intergroup comparison of baseline heart rate (beats/min.), 1 min. after ephedrine/control drug, one min. after induction and just after intubation. Values are expressed as mean ± standard deviation (SD)

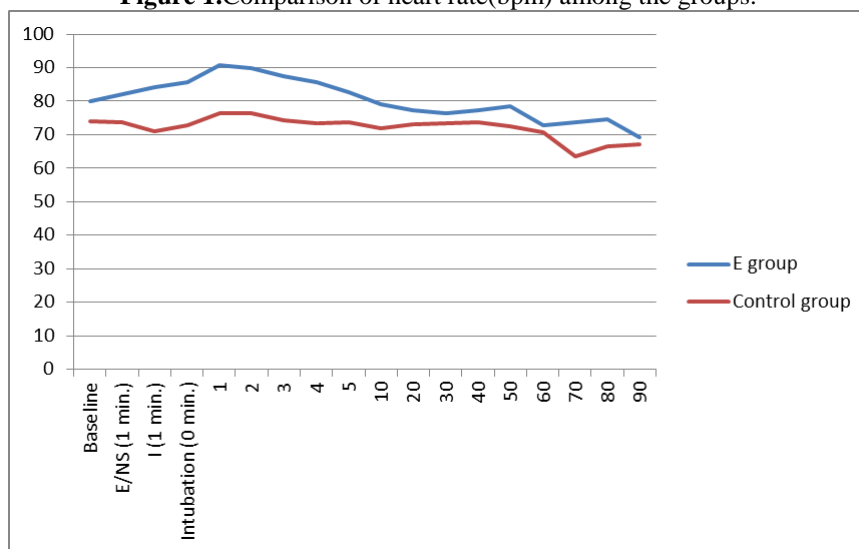
Heart rate	E group	Control group	P value
Baseline	80.03 ± 12.13	74 ± 12.04	>0.05
E/NS (1 min.)	82.03 ± 12.19	73.57 ± 11.33	0.007
I (1min.)	84.1 ± 13.04	71.07 ± 11.46	<0.01
I.T. (0 min.)	85.57 ± 12.6	72.83 ± 14.28	0.001

E = Ephedrine, NS = normal saline, I = Induction, I.T. = Intubation

The difference was highly significant after induction and this significant difference lasted upto five minutes after intubation with the ephedrine treated group showing increased heart rate compared to control group (figure 1). The difference was still significant but not highly significant at ten minutes (p value = 0.05) and ephedrine treated group showing increased heart rate. The difference in heart rate was insignificant after ten minutes and

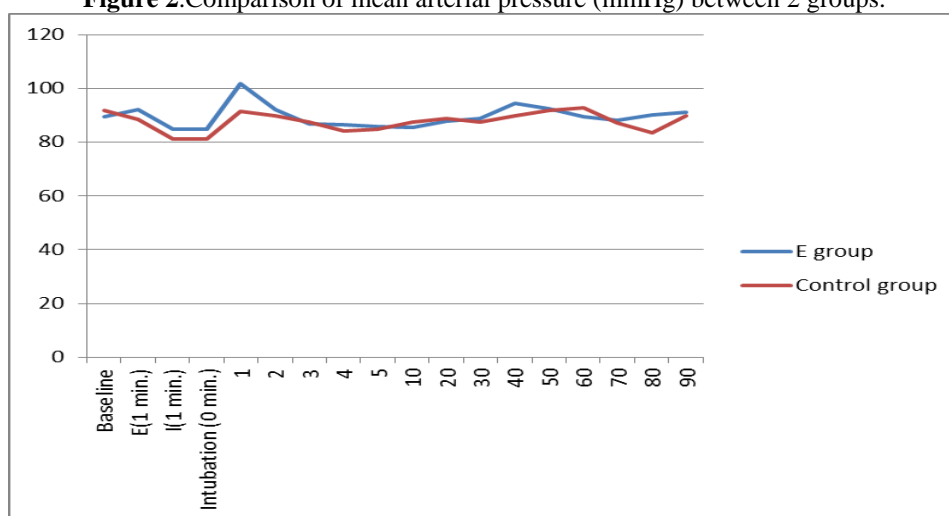
remained insignificant throughout surgery thereafter. However there was difference in baseline heart rate between two groups, with the ephedrine group having baseline heart rate of 80.03 ± 12.13 compared to 74 ± 12.04 in the control group. Therefore intragroup comparison of baseline heart rate was made, which show that there was no significant difference in heart rate, one minute after administration of study drug in the ephedrine group, with p value of 0.094. Similarly the difference in heart rate was insignificant in control group, one minute after receiving control drug i.e. normal saline ($p = 0.777$). The difference remained insignificant throughout surgery in the control group, but the difference in heart rate was significant, one minute after induction and just after intubation in the group receiving ephedrine ($p = 0.030$ and 0.009 respectively). The difference became highly significant upto two minutes after intubation and thereafter p value gradually increased ($p = 0.005$) at four minutes after intubation.

Figure 1. Comparison of heart rate (bpm) among the groups.



There was no significant difference in heart rate from baseline at five minutes of intubation and thereafter, in the intragroup comparison of ephedrine group. Figure 2 shows comparison of mean arterial pressure between two groups. There was no significant difference in baseline mean arterial pressure between two groups and p value was 0.29. Also there was no significant difference in MAP, one minute after ephedrine/NS, one minute after induction and just after intubation. P values were 0.18, 0.21 and 0.106 respectively. However there was significant difference in mean arterial pressure one minute after intubation, with mean \pm SD of 101.63 ± 11.49 in ephedrine group as compared to 91.53 ± 11.68 in control group and p value was 0.001. However thereafter, there was no statistical significant difference in mean arterial pressure between two groups throughout surgery.

Figure 2. Comparison of mean arterial pressure (mmHg) between 2 groups.



Similar results were seen in systolic blood pressure comparison between two groups . Systolic blood pressure at one minute after intubation was 135.6 ± 16.7 in the ephedrine group as compared to 120.6 ± 16.4 in the control group and p value was 0.001. However there was no significant difference in baseline systolic blood pressure, one minute after drug administration, one minute after induction and immediately after intubation. The difference was also insignificant two minutes after intubation and thereafter throughout surgery. Diastolic blood pressure showed significant difference just after intubation, with mean \pm SD of 68.23 ± 7.96 in the ephedrine group, compared to 63.4 ± 9.0 in the control group and p value was 0.033. At one minute after intubation, the values of mean \pm SD were 80.13 ± 10.73 in ephedrine group and 74.17 ± 12.45 in control group and p value was 0.052. At all other times during surgery, the p values were insignificant for diastolic blood pressure except at 60 minute after surgery, which may be a error due to small sample size in the study.

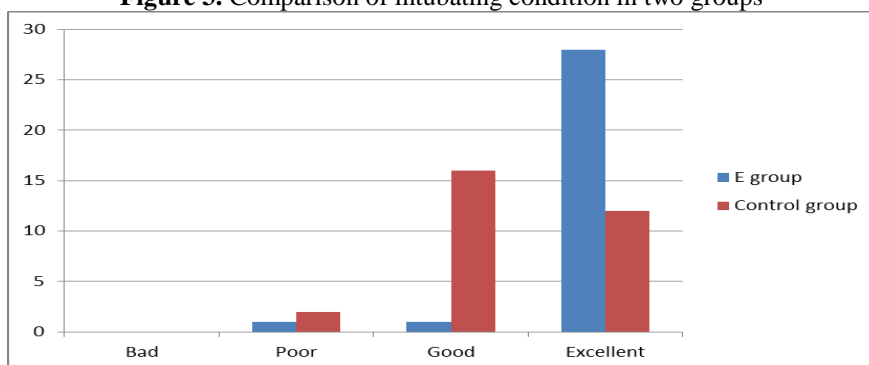
Table 2. Comparison of onset time, intubating conditions and duration of single dose of rocuronium. Values are expressed as mean \pm standard deviation.

Variable	E group	control group	P value
I.T.(sec.)	67.67 \pm 30.36	150.33 \pm 49.72	< 0.01
I.S.	8.47 \pm 0.86	7.4 \pm 1.037	< 0.01
I.A.	1.2 \pm 0.55	1.03 \pm 0.18	> 0.05
T. time (min.)	37.7	38.6 \pm 5.06	0.013
S.T.R. at 20 sec.	43.67 \pm 12.89	55.77 \pm 14.6	< 0.01
30	31.6 \pm 12.3	47 \pm 13.8	< 0.01
40	21.6 \pm 12.1	40.4 \pm 12.9	< 0.01
50	14.9 \pm 8.9	34.4 \pm 12.5	< 0.01
60	10.97 \pm 7.78	29.7 \pm 11.1	< 0.01
70	9.2 \pm 6.5	25.1 \pm 10.4	< 0.01
80	8.2 \pm 5.7	21.7 \pm 10.1	< 0.01
90	6.2 \pm 4.9	20.7 \pm 8.04	< 0.01
100	4.68 \pm 4.7	18.3 \pm 5.8	< 0.01
110	4.38 \pm 4.8	16.7 \pm 5.5	< 0.01
120	4.7 \pm 4.67	14.8 \pm 5.4	< 0.01
I.T : Intubation time, I.S: Intubation score, T. time = duration of effect of single dose of rocuronium, S.T.R. = Single Twitch Response, E = ephedrine.			

A highly significant difference was seen in the intubation time between two groups characterized by more than or equal to 90% decrease in single twitch response. Mean \pm SD values were 67.67 ± 30.36 for group receiving ephedrine as compared to 150.33 ± 49.72 in the control group and p value was < 0.001 (table 2). These values suggest that onset time of rocuronium is significantly decreased by prior administration of ephedrine.

There was highly significant difference in intubating conditions between two groups (figure 3). Intubation scoring was done according to the assessment of the ease of laryngoscopy manifested by jaw relaxation, the position of vocal cords and the reaction to tracheal intubation and cuff inflation as described by Cooper et al.16 (1992). and it was seen that excellent intubating conditions were met with the group receiving ephedrine.

Figure 3. Comparison of intubating condition in two groups



Intubation scoring was done according to above mentioned table and mean \pm SD was 8.47 ± 0.86 in the ephedrine group, compared to 7.4 ± 1.037 in the control group and p value was < 0.001 . However there was no significant difference between intubation attempts and duration of effect of rocuronium between two groups. Single twitch response showed highly significant difference between two groups, which was measured from twenty sec. after giving rocuronium till complete suppression of twitch response.

IV. Discussion

Ephedrine sulphate is a potent sympathomimetic that stimulates both alpha and beta receptors. The rate of onset of neuromuscular blockade depends on the rate at which a pharmacologically effective concentration is achieved in the biophase (neuromuscular junctional cleft), which in turn is influenced by potency of the drug, the dose given and the cardiovascular status, including cardiac output and muscle blood flow⁷⁻⁹. Ephedrine can produce an increase cardiac output and muscle blood flow^{10,11}.

Ephedrine in doses of 70, 140, 210 and 260 mcg/kg, has been effective in prevention of hypotension after induction with propofol^{12,13}. In our study we used the smallest dose (70 mcg/kg), so as to minimize the possibility of adverse effects associated with higher doses and we found that ephedrine in the dosage of 70 mcg/kg, given one minute before induction, significantly shortens the onset time of rocuronium bromide (67.67 ± 30.36 vs 150.33 ± 49.72 with p value < 0.001) as compared to control group. This finding is consistent with the studies done earlier^{14,2,15-16,17}. Hernan R Munoz et al¹⁶ observed similar findings by using ephedrine 70 mcg/kg before induction in study group. they also found significant reduction in the onset time of rocuronium 72 ± 19 s vs 72 ± 19 s compared to placebo when using ephedrine prior to induction.

In another study done by Han DW et al¹⁸ in 2008 on the significance of injection timing of ephedrine before induction, the onset time of rocuronium 0.6 mg/kg was found to be 80 ± 21 in the control group compared to 64 ± 15 and 72 ± 11 in ephedrine treated groups. We also found that ephedrine improves the intubating conditions significantly. In the ephedrine treated group, more than 93% patients had excellent intubating conditions against 40% in control group, 3% had good intubating conditions (53% in control group), while only 3% were faced with poor intubating conditions (6% in control group).

In a study done by M.D. Gopalakrishna et al¹⁹ in 2007 using propofol 2.5 mg/kg and rocuronium 0.6 mg/kg, given one minute after ephedrine, during rapid tracheal intubation, it was found that intubating conditions were significantly better with ephedrine. But findings in their study were not supported by neuromuscular monitoring. Whereas in our study, we used single twitch response and the findings of neuromuscular monitoring in our study do support the hypothesis that the ephedrine pre-treatment improves the intubating conditions by shortening the onset of action of rocuronium. A significant difference in single twitch response was observed, starting from 20 seconds after giving rocuronium till intubation (p value < 0.001).

In our study, we did not measure muscle blood flow. So we can only speculate as to whether this variable was increased by ephedrine, and whether this was the mechanism for the improvements observed in the intubating conditions. Rocuronium when used in lower dose of 0.6 mg/kg for rapid tracheal intubation provides suboptimal conditions in 20-25% of patients²⁰. This may be due to a decrease in cardiac output caused by the induction agent resulting in slower onset of action at the laryngeal muscles and the diaphragm. Ephedrine, by increasing cardiac output may result in faster delivery of rocuronium to the laryngeal and diaphragmatic muscles and this may shorten the onset time of rocuronium and improve intubating conditions.

On the basis of this hypothesis, ephedrine given before the induction agent was found to improve the intubating conditions. Ephedrine reaches its peak effect in two to three minutes and exerts its effect in less than two minutes after administration²¹. Another important finding, in our study was that there was statistically significant difference in heart rate among the groups during the first five minutes after intubation (p < 0.001). Heart rate increase compared to baseline was more in the group receiving ephedrine than in the control group not receiving ephedrine. But significant increase in heart rate lasted for five minutes only and thereafter, the

heart rate gradually settled to near baseline value. Heart rate gradually increased from 80.03 ± 12.13 to 82.03 ± 12.19 , 84.1 ± 13.04 , 85.5 ± 12.6 and 90.7 ± 13.4 (one min. after intubation) and then gradually decreased thereafter reaching 79.1 ± 9.4 after ten minutes of intubation in the group receiving ephedrine.

These results are also comparable with the previous studies^{16,21-23}. However, there was no statistically significant difference in mean arterial, systolic and diastolic blood pressures except at one minute after intubation. But, caution needs to be exercised in the subset of patients in whom ephedrine-induced tachycardia might be detrimental (e.g. patients with ischemic heart disease). The similar results has been seen in earlier studies¹⁹. M.D. Gopalakrishna et al¹⁹ in their study on ephedrine found that despite ephedrine pre-treatment, there was a decrease in mean arterial pressure in the immediate post-induction period. There was no clinically significant difference in mean arterial pressure and heart rate among the groups during the first 5 min after intubation (considering 20% change as clinically significant). In contrast with the study done by Tan et al²² (2002), we did not find any significant increase in mean arterial pressure in the ephedrine group except for an increase in heart rate associated with the use of ephedrine. In our study we did not find any adverse effect after the administration of ephedrine, but it must be considered that in a sample of thirty patients having an incidence of adverse effect equal to zero, the upper limit of the 95% confidence interval is estimated in 10%²⁴.

V. Conclusion

Pre-treatment with ephedrine 70 mcg/kg reduces the onset time of rocuronium and improves the intubating conditions without significant adverse effects in a group of relatively healthy patients and the combination of ephedrine, propofol and rocuronium can be valueable when succinylcholine is contraindicated and the shortest possible time from loss of consciousness to tracheal intubation is required.

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