ORIGINAL ARTICLE

The effect of dopamine pre-treatment on intubating conditions and haemodynamics during rapid tracheal intubation using propofol and rocuronium

Sandip Sinha[1], Manjushree Ray[2], Maitreyee Mukherjee[3], Sajib Chatterjee[4], Avijit Hazra[5], Nabanita Das[6]

[1]*Assistant Professor,* [2]*Professor and Head,* [3]*RMO cum clinical tutor,* [5]*Associate Professor,* [6]*PG student,*
Department of Anaesthesiology, Institute of Post Graduate Medical Education and Research (IPGMER), 244, Acharya Jagadish Chandra Bose Road, Kolkata-700020.

[4]*RMO cum clinical tutor, Department of General Surgery, NRSMCH, West Bengal (India)*

Correspondence: Dr. Sandip Sinha, 16/D Rishi Bankim Street, P.O. Konnagar, Dist. Hooghly, West Bengal 712235 (India); Phone: 09831865165; e-mail: dr.sandipsinha72@yahoo.in

ABSTRACT

Aims and Objectives: To assess intubating conditions and haemodynamic changes in patients pre-treated with dopamine during rapid tracheal intubation using rocuronium and propofol.

Methodology: Forty adult patients of ASA I and II, aged 20–60 years, scheduled for elective as well as emergency surgery, were included in this prospective randomized open label group double blind study. In Group A patients injection dopamine infusion 3 μg/Kg/min and in Group B patients an equal volume of normal saline was infused over 15 minutes before administering general anesthesia using propofol 2 mg/Kg and rocuronium 0.6 mg/Kg . Laryngoscopy and tracheal intubation was attempted at 60 seconds, whereby anaesthesiologist assessed the intubating conditions.

Duration of laryngoscopy , Train of four ratio (TOF ratio) at 60 sec after rocuronium administration, time from disappearance of all four twitches on TOF count, intubation score at 60 seconds were recorded. Mean arterial pressure, pulse rate and oxygen saturation were recorded at different time points.

Results: Intubating conditions at 60 seconds were significantly better in Group A than in Group B patients. Haemodynamic parameters were not significantly altered in Group A. Time taken for intubation was significantly lower in Group A than in Group B.

Conclusion: Dopamine pretreatment improves intubating conditions after rocuronium injection without significantly altering haemodynamic parameters.

Keywords : Rapid sequence induction; dopamine pre-treatment; rocuronium; propofol

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INTRODUCTION

During the rapid sequence induction of general anaesthesia, the use of a muscle relaxant with a rapid onset time is crucial to reduce the risk of hypoxia and aspiration pneumonia. Although succinylcholine is an excellent choice for the purpose, its many potential complications has lead to the search for an alternative. In addition to the development of a new muscle relaxant for rapid tracheal intubation, efforts have been made to reduce the onset time of existing non depolarising muscle relaxant (NDMR).

To reduce the onset time, many studies were focussed on modifying haemodynamic factors such as the cardiac output, the circulation time and the muscle blood flow.[1] Researchers have suggested that a NDMR may act more rapidly on the neuro-muscular (NM) junction through increased cardiac output and muscle blood flow, because the agent injected in the vein may

reach to the NM junction more rapidly.[2.]

Rocuronium is the currently preferred non-depolarizing agent used as an alternative to succinylcholine for rapid tracheal intubation.[3] Recognizing the problem of prolonged duration of action with larger doses, attempts were made to decrease the dose of rocuronium without compromising on its onset time or intubating conditions.[4] Thus the use of ephedrine during the induction of general anesthesia has been described to accelerate the onset of action of rocuronium and improve the intubating condition.[5-8] . Dopamine has been shown to exhibit a graded pharmacological response, with a dose-dependent predominant activation of dopaminergic receptors, □-receptors and □-receptors. At doses <3 $\mu g/kg/min$, dopamine has been found to activate dopamine A1 receptors, which cause vasodilation of the renal arteries and other vascular beds, including mesenteric, coronary, and cerebral beds. In addition, there is stimulation of dopamine A2 receptors that leads to inhibition of norepinephrine release from sympathetic nerve endings.[17] Activation of dopamine A1 and A2 receptors also results in a decline in systemic vascular resistance and an increase in renal blood flow. Dopamine infused at approximately 3 to 5 $\mu g/kg/min$ activates □1- and □2-adrenergic receptors, conferring a positive inotropic effect that is responsible for the increase in cardiac output. This □-adrenergic receptor induced increase in cardiac output and tissue perfusion results in faster delivery of rocuronium to the neuromuscular junction of the laryngeal and diaphragmatic muscles which might shorten the onset of action of rocuronium and improve the intubating conditions. Also the introduction of rocuronium at the point when the cardiac output was increased by dopamine effectively reduced the onset time. In this study we have administered dopamine 15 minutes prior to induction of anesthesia and assessed the intubating condition one minute after administration of rocuronium bromide.

We conducted this study to find out the effect of dopamine infusion on intubating condition at 60 seconds following administration of rocuronium bromide (0.6 mg/kg) and the haemodynamic changes associated with induction of anesthesia and endotracheal intubation.

METHODOLOGY

This single centre, prospective randomized open label group double blind study was conducted at the Department of Anesthesiology at Institute of Post Graduate Medical Education and Research, Kolkata for 11 months.

Forty ASA grade I and II patients, aged 20-60 years, scheduled for elective and emergency surgical procedures were included in the study. Patients with hypertension, cardiovascular diseases, neuromuscular disorders, anticipated difficult airway, morbid obesity, increased risk of pulmonary aspiration, on drugs that influence NM blocking agents or those with known allergy to the drugs, as well as pregnant female patients were excluded.

The rate (%) of successful intubation at 1 minute was taken for the primary outcome measure for this study assuming this rate will be at the best 10% for the normal saline group (Group B) and at least 60% for the dopamine pre-treated group (Group A), it was calculated that 17 subjects will be required per group with order to detect this 50% difference with 90% power and 5% probability of type I error. Rounding at the required subject was kept at 20 persons per group.

Patients were randomized into two groups, Group A and Group B, each group containing 20 patients. Randomization was generated by the statistical software "Microsoft Excel XPTM (2003)". Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001] and MedCalc version 11.6 [Mariakerke, Belgium: MedCalc Software 11.6] was used to analyse the data. Comparison of numerical variables between Group A and Group B – was done by Student's t test and Mann-Whitney U test was used to analyse the numerical variables. Repeated measures ANOVA with post-hoc Tukey's test was used to see any change of haemodynamics within groups.

Written, informed consent was obtained from each patient prior to including him or her in the study. The anesthesiologist performing the laryngoscopy and endotracheal intubation and the anesthesiologist administering the drugs both were blinded to the group allocation.

All the patients were fasted for at least 8 hours for solid food and 3 hours for clear fluid. On arrival in the OR, standard monitoring devices such as five leads electrocardiogram (ECG), automated noninvasive arterial pressure by oscillometry, pulse oximetry and N-M monitors were instituted. Intravenous access was obtained and infusion of lactated Ringer was started at a rate of 2 ml/kg/hr. All the patients were premedicated with injection fentanyl 2μg/kg ten minutes before induction. Group A patients received 3 $\mu g/kg/min$ of dopamine hydrochloride by syringe pump. Fifteen milligram dopamine was added to 50 ml normal saline. Thus each ml solution contained 0.3mg or 300 μg dopamine. This solution was infused at a rate of 0.01 ml/kg/min for 15 minutes. Group B patients received 0.01 ml/kg/min of normal saline for 15 minutes as a control group. Subsequently both Group A and Group B patients were administered general anaesthesia using propofol 2 mg/kg over 20 sec and rocuronium 0.6 mg/kg 10 seconds later.

Just before the administration of propofol, Train of four (TOF) ratio monitoring in response to ulnar

nerve stimulation was begun using TOF-GUARD. Laryngoscopy and tracheal intubation was attempted by an expert anaesthesiologist (with at least 3 years of experience) who was blinded to the group allocation, with an appropriate sized Macintosh blade 60 sec after administration of rocuronium. The anaesthesiologist also assessed the intubating conditions as per the intubation scoring system of the Consensus Conference on Good Clinical Research Practice in Pharmacodynamic Studies of Neuromuscular Blocking Agents, Copenhagen Consensus.[9] Oral tracheal tubes (7.0 and 8 mm, internal diameter) were used for female and male patients, respectively. The cuff was inflated with air until the disappearance of a palpable leak on positive pressure ventilation. In Group A patients dopamine infusion and in Group B patients normal saline infusion was stopped just after intubation.

Successful intubation was defined as a condition when each score of three components was more than 2 points. Failed intubation was defined if any component showed less than 2 points.

Table 1: Intubation scoring system according to Viby Mogensen

Score	Vocal cord	Jaw relaxation	Coughing or bucking
3	Fully abducted	Fully relaxed	Nil
2	Slightly abducted	Slightly stiff	Slight
1	Partially abducted	Stiff	Moderate
0	Closed	Impossible to open	Severe

Anaesthesia was maintained with oxygen 33%, nitrous oxide 66% and isoflurane 0.5-1% with positive pressure ventilation maintaining normocapnia.

Patient's mean arterial pressure (as recorded by NIBP), heart rate (as displayed by the electrocardiogram monitor) and oxygen saturation were recorded prior to administration of the study drug (baseline), at 5 min, at 10 min after starting the drug infusion, just before and after intubation, and at 1min, 3min and 10min after intubation.

A 20% change in haemodynamic variables from the baseline value was regarded as significant and managed by the concerned anaesthesiologist at their discretion.

The duration of laryngoscopy (the time from the insertion of the laryngoscope blade into the patient's mouth to its removal after successful intubation), TOF ratio (ulnar nerve stimulation; adductor pollicis response to supramaximal stimuli) at 60 sec after rocuronium administration using TOF-GUARD, time from the disappearance of all four twitches on TOF count, reaction of the patients to tracheal intubation and intubation score at 60 seconds were recorded.

RESULTS

Total forty patients were needed for the study. There were no statistical significant differences among the groups in terms of demographic data (p > 0.05). Table 2 shows comparison of demographic and ASA Grade profile between the groups.

Table 2: Comparison of demographic profile between the groups

Parameter	Group A n=20	Group B n=20	p value
Age (Years) Mean±SD	37.95±10.42	41.15±12.81	0.391
Weight (Kg) Mean±SD	50.95±4.18	50.8±5.41	0.922
ASA Grade I II	11 (55%) 9 (45%)	13 (65%) 7 (35%)	0.748
Sex (M:F)	12:8 (60:40%)	10:10 (50:50%)	0.751

Table 3 compares the haemodynamics between the groups at various time points. Baseline haemodynamics (Mean Arterial Pressure-MAP, Pulse Rate-PR) were comparable between the groups with no statistical significant differences.

Just before intubation, there was a significant increase in PR in Group A (82.15) when compared with Group B (74.10) (p < 0.05). Apart from this, haemodynamics (MAP, PR) were comparable between the groups with

Table 3: Haemodynamic profile (mean ± SD)

	Mean Arterial Pressure (mmHg)			Pulse rate (beats per minute)		
	Group A ()	Group B	p-value between groups	Group A	Group B	p-value between groups
Before infusion	73.17±6.70	71.16±9.25	0.511	73.36±6.17	72.9±14.62	0.801
5 min after infusion	74.30±5.22	71.65±9.32	0.463	76.11±5.26	74.45±5.47	0.713
10 min after infusion	77.21±6.46	73.35±9.99	0.121	78.20±5.16	74.23±5.53	0.110
before intubation	78.33±6.05	73.08±6.86	0.078	82.15±4.52	74.10±8.78	0.004
1 min after intubation	81.15±8.55	85.35 ±12.57	0.093	85.55±7.05	87.10±5.26	0.529
3 min after intubation	78.65 ±10.95	81.21±7.72	0.351	78.54±4.43	82.00±3.58	0.135
10 min after intubation	74.63±6.74	75.6±5.08	0.764	74.10±5.52	76.32±6.45	0.519
p-value within group	< 0.001	0.003		0.001	<0.001	

‚p-value within group comes from repeated measures

no statistical significant differences at various time points. SpO2 values were comparable among the groups at different time points. Within group comparison of MAP and PR showed significant differences across time both in Group A and in Group B (Table 3) but within group comparison of SpO2 did not reveal any significant differences across time.

The duration of laryngoscopy is significantly lower in Group A (13.9±2.29 sec.) than in Group B (23.3±4.40 sec.) (p<0.05).

Mean TOF count at 60 sec in Group A is 64.25±7.30 and in Group B is 81.25±6.66 (p<0.05). TOF disappearance time in Group A is 169.65±7.22 and in Group B is 226.05±29.97 (p<0.05).

Intubation score at 60 seconds is significantly higher in Group A (8±0.64) than in Group B (4±0.99) (p<0.05).

Table 4: Comparison of onset and quality of neuromuscular block (mean±SD)

Onset and quality of block	Group A	Group B	p-value
Intubation score at 60 sec	8±0.64	4±0.99	
TOF ratio at 60 sec	64.25±7.30	81.25±6.66	0.000
TOF disappearance time (sec)	169.65±7.22	226.05±29.97	
Duration of laryngoscopy (sec)	13.90±2.29	23.30±4.40	

DISCUSSION

Recognizing the problem of prolonged duration of action with larger doses (1 mg/kg), attempts were made to decrease the dose of rocuronium(0.6 mg/kg) without compromising on its onset time or intubating conditions. Thus, pre-treatment with dopamine infusion (3 μg/kg/min) during the induction of general anaesthesia was found to accelerate the onset of action of rocuronium and improve the intubating condition. However, there were no clinically significant differences in mean arterial pressures and heart rates among the groups during the first 10 minutes after intubation. Rocuronium used in the lower dose of 0.6 mg/Kg for rapid tracheal intubation is known to provide suboptimal intubating conditions in 20–25% of patients.[10] This could be as a result of a decrease in cardiac output caused by the induction agent resulting in slower onset of action at the laryngeal muscles and the diaphragm.

The onset time of a neuromuscular blocking agent is partly determined by the speed with which the drug reaches the neuromuscular junction, a factor that appears to be proportional to cardiac output and muscle blood flow. Studies using induction agents that maintain cardiac output and arterial pressure (i.e. etomidate and ketamine) have suggested that the use of these drugs was associated with faster onset of action and better intubating conditions with rocuronium.[11,12] Ephedrine, by stimulating the β-adrenergic recepter, increases the cardiac output and tissue perfusion, which results in faster delivery of rocuronium to the neuromuscular junction of the laryngeal and diaphragmatic muscles which might shorten the onset of action of rocuronium and improve the intubating conditions.[3,13,14.] As an indirect evidence, Han et al[14] reported that the introduction of rocuronium at the point when the cardiac output was increased by ephedrine effectively reduced the onset time. In addition, another study using esmolol, which is a β_1-adrenergic antagonist, reported that the onset time of rocuronium was delayed when esmolol was introduced before the settlement of rocuronium. These studies support the fact that the effect of a β-adrenergic receptor agonist oriented by the ephedrine served a significant role in accelerating the onset time.[13,15.] On the basis of this hypothesis, pre-treatment with dopamine during propofol induction was found to improve the intubating conditions with rocuronium 0.6 mg/ Kg.

The results of our study were similar to the findings of the earlier studies using ephedrine.[3] Dopamine has been shown to exhibit a graded pharmacological response, with a dose-dependent predominant activation of dopaminergic receptors, α-receptors, and β-receptors.[16,17] Generally, at doses <3 μg/Kg/min, dopamine has been found to activate dopamine A1 receptors, which cause vasodilation of the renal arteries and other vascular beds, including mesenteric, coronary, and cerebral beds. In addition, there is stimulation of dopamine A2 receptors that leads to inhibition of norepinephrine release from sympathetic nerve endings.[17] Activation of dopamine A1 and A2 receptors also results in a decline in systemic vascular resistance and an increase in renal blood flow. Dopamine infused at approximately 3 to 5 μg/Kg/min activates β_1 and β_2-adrenergic receptors, conferring a positive inotropic effect that is responsible for the increase in cardiac output and tissueμ perfusion, which results in faster delivery of rocuronium to the neuromuscular junction of the laryngeal and diaphragmatic muscles which in turn results in shortening of the onset of action of rocuronium and thereby improves the intubating conditions. At a dose >5 μg/Kg/min, dopamine has been reported to exert clinically relevant activation of α_1 and α_2-adrenergic receptors, which results in arterial vasoconstriction. Thus, dopamine in the greater dosages (>5μg/Kg/min) produce vasoconstriction of

blood vessels supplying laryngeal muscles, thus limiting the access of the relaxant to its site of action.

In our study we included patients scheduled for both elective and emergency surgical procedures. Rapid sequence intubation was needed in emergency surgical patients with full stomach. To remove the bias, we adopted similar technique and sequence in all of the patients.

The findings of neuromuscular monitoring in our study support the hypothesis that the dopamine pre-treatment improves the intubating conditions by shortening the onset of action of rocuronium. The times for disappearance of all four twitches on TOF count and the TOF ratio at the end of 60 seconds of rocuronium injection were significantly higher in Group B than in Group A. The lack of agreement between the blockade characteristics at the laryngeal muscles and the adductor pollicis is well demonstrated in the literature. [18 – 21.] However, as the site of monitoring was the same in all four groups, the results can still be compared for the difference in onset of neuromuscular block. Heart rate increased in all the dopamine pre-treated patients in

our study. This is similar to the findings of the earlier studies using ephedrine.[5,6.]Thus,caution needs to be exercised in the subset of patients in whom dopamine-induced tachycardia might be detrimental (e.g. patients with ischaemic heart disease). In such cases the risk of tachycardia has to be weighed carefully against the benefit of improved intubating conditions. There was no clinically significant difference in mean arterial pressure and heart rate among the groups during the first 10 min after intubation (considering 20% change as clinically significant). Thus, prophylactic dopamine pre-treatment only attenuates, but does not completely abolish the decrease in arterial pressure associated with induction of anesthesia using fentanyl and propofol. This is similar to the findings of the earlier studies using ephedrine.[5]

CONCLUSION

We conclude that pre-treatment with dopamine 3 μg/Kg/min for 15 minutes improves the intubating conditions during rapid tracheal intubation using propofol and rocuronium, without significantly altering haemodynamic parameters.

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