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Effects of Ephedrine on the Onset of Neuromuscular Block and Hemodynamic Responses Following Priming by Atracurium

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Abstract: In a double blinded study, seventy ASA I and II patients, undergoing elective surgery under general anesthesia were randomized into two equal groups. In both groups, 2 μg kg^{-1} fentanyl was injected as premedication. Anesthesia was induced by 1.5 mg kg^{-1} of propofol and subsequently was maintained with a propofol infusion at a rate of 8 mg kg^{-1} h^{-1}. After control-TOF obtained and recorded by accelerometer, priming dose of atracurium 0.05 mg kg^{-1} was injected intravenously and 2.5 min later, intubating dose of atracurium 0.5 mg kg^{-1} with 140 μg kg^{-1} ephedrine in study group or equal volume of the saline in control group were injected. When TOF ratio became zero, patients tracheas were intubated. Variables were noted as: heart rate and blood pressure as baseline, 1, 3, 5 min after induction and one minute after intubation and onset time of atracurium when TOF ratio became zero. Data were analyzed by Independent sample t-test, Chi-square, Mann-Whitney U-test and Repeated measures ANOVA. $p<0.05$ was considered statistically significant. Onset time of atracurium for intubation was shorter in ephedrine group ($p = 0.0001$). The baseline values of Mean Arterial Pressure (MAP) and Heart Rate (HR) did not differ between the two groups. HR and MAP at first and third minutes after induction were lower than baseline in each group ($p = 0.0001$). There was significant statistical (not clinical) difference in mean HRs between the two groups ($p = 0.003$).The difference of mean MAPs was not statistically significant between the two groups ($p = 0.213$). Ephedrine, accelerated the onset time of atracurium in priming technique, with minimal hemodynamic effects.

Key words: Ephedrine, atracurium, neuromuscular block, hemodynamic response, priming

INTRODUCTION

During the onset time of neuromuscular blocking agents for intubation, the patient is exposed to the risk of hypoxia and pulmonary aspiration. Since succinylcholine, a short onset depolarizing muscle relaxant, has numerous adverse effects including: hyperkalemia, cardiac dysrhytmias, fasciculation, increased intraocular and intragastric pressure, allergic reaction and trigger malignant hyperthermia; various strategies have been used to shorten the onset time of other muscle relaxants for rapid intubation, including increasing the dose and priming technique. In priming technique, administration of a small sub-paralyzing dose, several minutes before the intubating dose, the onset of Non Depolarizing Muscle Relaxant (NDMR) will accelerated. These alternates may provoke a long duration of muscle paralysis or muscle weakness before induction of anesthesia (Bragg *et al*., 1994; Kopman *et al*., 2001; Miller, 2005; Mencke *et al*., 2006).

The onset time of neuromuscular blocking drugs is partially determined by circulating factors, including muscle blood flow and cardiac out put (Donati, 1988; Leykin *et al*., 2005). Ephedrine can increase cardiac output and therefore muscle blood flow (Lawson and Meyer, 2001).

Szmuk *et al*. (2000) reported that significant reduction of the onset of rocuronium in patients pretreated with ephedrine but Kumatsu *et al*. (2003) reported that ephedrine fails to accelerate the onset of neuromuscular block by vecuronium.

Premedication with 10 mg of ephedrine decreased the onset time of rocuronium but did not affect that of atracurium (Santiveri *et al*., 2003).

Since in our country rocuronium is not available and vecuronium and mivacurium are scarce or very expensive, we used atracurium, the most frequent NDMR available in our operating rooms. We tested the hypothesis that when ephedrine added to atracurium in priming technique, it will accelerate the onset time of atracurium with minimal hemodynamic effects. So we can use it instead of succinylcholine or other NDMRs and reduce the cost and side effects.

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MATERIALS AND METHODS

This randomized clinical trial was performed in Dr. Shariati Hospital of Tehran University of Medical Sciences during February to July of 2006. The study protocol conformed to the ethical guidelines of the 1989 Declaration of Helsinki.

After Institutional Ethics committee approval, each patient's informed written consent, was obtained separately. Seventy patients were included in the study. Inclusion criteria were ASA class I and II, age 20-60 years and elective surgery under general anesthesia.

American Society of Anesthesiologists (ASA) classification for risk of anesthesia based on the physical condition of the patient independent of the planned operation. ASA I: a normal healthy patient, ASA II: a patient with mild systemic disease that results no functional limitation.

Exclusion criteria included the presence of cardiovascular or neuromuscular diseases, any medications known to affect neuromuscular function, anticipated airway difficulties and risk of pulmonary aspiration.

On arrival in the operating room, ECG electrodes were applied and oxygen saturation was monitored by pulse oxymeter. An 18-G IV cannula was inserted into a vein of the patient's hand and 5 mL kg^{-1} lactated Ringer's solution was infused. Base line heart rate (HR) and Non Invasive Blood Pressure (NIBP) were measured and 2 μg kg^{-1} fentanyl (Amp 10 mL, Fentanyl-Janssen™, Belgium) was injected as premedication. After one minute, anesthesia was induced by 1.5 mg kg^{-1} of propofol (Amp 20 mL, Propofol 1% Fresenius™, Germany) administered over 10 seconds and subsequently was maintained with a propofol infusion at a rate of 8 mg kg^{-1} h^{-1}.

The patients were randomly assigned to receive 140 μg kg^{-1} ephedrine (Amp mL = 50 mg, Ephedrin Streuli™, Switzerland) (n = 35) or an equivalent volume of saline (n = 35). Randomization was based on computer-generated codes that was concealed until interactions were assigned. The coded syringes of saline or ephedrine were prepared by an independent anesthetist in a total volume of 5 mL there fore both the anesthesiologist and the patient was blinded to the group assignment.

After unconsciousness and during nerve stimulation patients were ventilated manually via a face mask with 100% oxygen. Neuromuscular function was monitored immediately by using accelerometer (TOF Guard, XAVANT Technology®, UK Ltd).

The ulnar nerve of the arm contralateral to the IV cannula was stimulated for finding supramaximal stimulation through surface electrode with a single square-wave pulse of 0.2 m sec in duration. After control-TOF was obtained, priming dose of atracurium (Amp 10 mg mL^{-1} Mayne Pharma Plc™, UK) 0.05 mg kg^{-1} was injected intravenously. After 2.5 min, intubating dose of atracurium 0.5 mg kg^{-1} with 140 μg kg^{-1} ephedrine in study group or equal volume of the saline in control group were injected simultaneously over 30 sec.

Adductor pollicis contraction was measured with piezoelectric accelerometer fastened to the thumb. TOF stimulation was repeated at 10 sec intervals until TOF-ratio becomes zero. Then the patient was intubated by macintosh blade size 3-4 and tracheal tube number 7-7.5 for women and 7.5-8 for men, respectively.

The time interval between the intubating dose of atracurium to tracheal intubation was recorded. Non Invasive Blood Pressure (NIBP) and heart rate were recorded at base line (before premedication) and 1, 3, 5 min after propofol injection and 1 min after tracheal intubation. The presence of arrhythmia on the ECG monitor and other complications during priming interval were recorded.

Statistical analysis: Sample size calculation was based on detection a 35% difference in the onset time of atracurium (59 sec compared to 90 sec in priming technique) with $\alpha = 0.05$ and power = 90%. Normality of distribution was tested by Kolmogorov Smirnov test.

Data were analyzed by SPSS version 11.5 (SPSS Inc, Chicago, IL) and Independent sample t-test and Chi-square were used for comparison of demographic data. Time to maximum neuromuscular block between the two groups was compared with Mann-Whitney U-test. Repeated measures ANOVA was used for comparing (HR) and (MAP) differences within subjects and between the two groups. $p<0.05$ was considered statistically significant.

RESULTS

There were no significant differences in demographic data between the two groups, (Table 1) (Independent sample t-test, Chi square).

Onset time of atracurium for intubation (TOF ratio = 0) was significantly shorter in ephedrine group compared to saline group, the median (interquartile range) of it was 57 (45-71) and 80 (67-91) sec, respectively (Mann-Whitney U- test, p = 0.0001).

Ephedrine 140 μg kg^{-1} did not cause clinically unacceptable tachycardia or hypertension (30% more than base line value) in any patient.

The baseline values of MAP and HR did not differ between the two groups. Heart rate at first and third

Table 1: Demographics of the study groups (n=35 in each group)

Variables	Group 1 (ephedrine)	Group 2 (saline)
Age (year)*	37±15	34±12
Weight (kg)*	66±12	67±11
Sex (M/F)	14/21	18/17
ASA class (I/II)	23/12	20/15

*: Data are presented as mean±SD

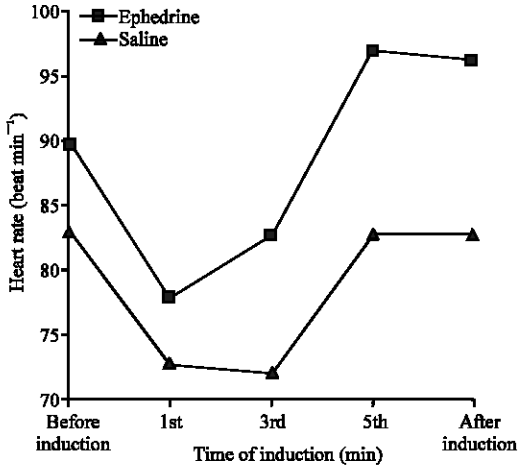

Fig. 1: Comparison the mean of heart rates between the study groups: before induction of anesthesia, 1st, 3rd and 5th min after induction and 1 min after tracheal intubation

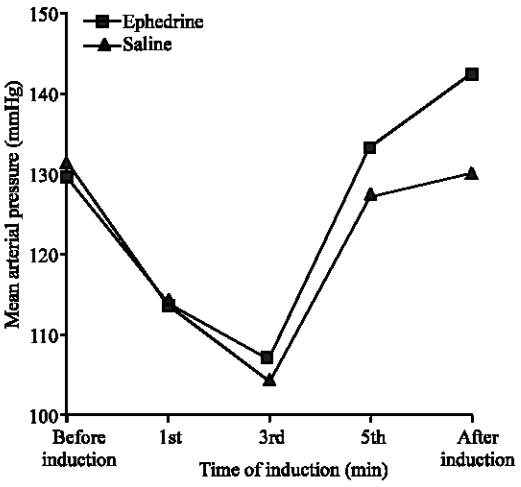

Fig. 2: Comparison the mean of MAPs (mean arterial pressures) between the study groups: before induction of anesthesia, 1st, 3rd and 5th min after induction and 1 min after tracheal intubation

min after induction were statistically lower than baseline in each group (repeated measures ANOVA, test of within subject effects, p = 0.0001) (Fig. 1).

There was statistically significant difference in the mean of HRs measured over time in ephedrine group (88.7±2.3, 95% CI: 84.2-93.2) compared to saline group (78.6±2.3, 95% CI: 74.1-83.2) (repeated measures ANOVA, test of between subject effects, p = 0.003).

Mean arterial pressure at first and third minutes after induction were statistically lower than baseline in each group (repeated measures ANOVA, test of within subject effects, p = 0.0001) (Fig. 2).

There was no significant statistical difference in mean of MAPs measured over time in ephedrine group (125.1±2.1, 95% CI: 120.8-129.3) compared to saline group (121.3±2.1, 95% CI: 117.1-125.6) (repeated measures ANOVA, test of between subject effects, p = 0.213).

During the priming interval no complications or arrhythmia were observed.

DISCUSSION

The main finding of this study is that the combination of ephedrine with priming dose of atracurium accelerated the onset time of atracurium without clinically acceptable complications.

The hemodynamic differences were statistically significant within each group but not between the two groups except for mean of HRs that was not clinically (30% more than base line value) significant.

The rational for combining the priming principle with ephedrine comprises partial occupancy of the cholinergic receptors by 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 near the onset time of other short onset of action muscle relaxants (Leykin, 2005).

Several studies noted the shortening effect of ephedrine pretreatment on the onset times of muscle relaxants such as vecuronium, rocuronium and succinylcholine that was correlated with this study (Szmuk *et al*., 2001; Ganidagli *et al*., 2004; Tan *et al*., 2002).

In the study by Komatsu *et al*. (2003), ephedrine failed to accelerate the onset of neuromuscular block by vecuronium that was not consistent with our study. This may be due to their administration of vecuronium after 11 min of stable propofol anesthesia to standardize the duration of control ulnar nerve stimulation. This type of administration caused depressed hemodynamic conditions that is not identical to typical clinical situation in which muscle relaxant is given just after propofol at induction, when BP and HR are higher.

Santiveri *et al*. (2003) compared the effects of 10 mg ephedrine on the onset time of atracurium compared with

rocuronium. They found that ephedrine decreases the time until onset of action of rocuronium but does not affect the timing of atracurium.This may be due to shorter onset time of rocuronium and low dose of atracurium (0.04 mg kg^{-1}) that they used for tracheal intubation.

We choose to give ephedrine at a dose of 140 μg kg^{-1} because larger dose could have caused an unacceptable increase in blood pressure and heart rate and also we didn't have cardiac index monitoring. Conversely, we did not choose a small dose of ephedrine because a dose of 70 μg kg^{-1} or less only slightly increase MAP and HR and can not improve muscle perfusion (Chow *et al*., 1998; Tan *et al*., 2002; Komatsu *et al*., 2003; Gamidagli *et al*., 2004).

In this study the combination of ephedrine and propofol did not induce clinically significant differences in both MAP and HR compared to saline group that was not correlated with Leykin *et al.* (2005). They have statistically significant increase in MAP and HR in ephedrine-rocuronium group compared to group without ephedrine, it may be due to their higher dose of ephedrine (210 μg kg^{-1}).

In conclusion ephedrine in dose of 140 μg kg^{-1} with propofol, accelerated the onset time of atracurium in priming technique with minimal hemodynamic effect. Limitations of this study are: we can not use ephedrine in hypertensive and ischemic heart disease patients, besides using NDMR in emergency situation and full stomach patients or anticipated difficult intubation may be dangerous.

Further studies may be needed for using this method with different dose of ephedrine and other non depolarizing muscle relaxants compared with short onset time of action muscle relaxants.

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