A Prospective Randomized Controlled Study of Sevoflurane's Effect on the Onset Characteristics and Intubating Conditions of Rocuronium under Routine Clinical Practice

Nazmeen I Sayed[1], Deepa Shriyan[2], Dipankar Das Gupta[3]

ABSTRACT

Introduction: The search for mechanism of "immobility" caused by volatile anaesthetics has been the forerunner for studies of their effect on neuromuscular junction. The aim of our study was to evaluate the effect of co- administration of sevoflurane on the intubating conditions and onset characteristics of rocuronium, during routine intravenous induction of anaesthesia.

Material and methods: 60 adult patients were randomly divided in sevoflurane and control group of 30 each. After induction patients in sevoflurane group were ventilated with 2% inspired concentration of sevoflurane in a fresh gas flow of 5l containing 66.66% nitrous oxide and 33.33% oxygen and patients in control group were ventilated without sevoflurane. Intubating conditions of the trachea at 2 mins after 0.6mg/kg of rocuronium were assessed.

Results: No significant difference was found in any of the parameters between the two groups. Sevoflurane and control group had clinically acceptable intubating conditions of the trachea in 28 (93.3%) and 25 (83.3%) of patients respectively (p = 0.42). The lag time of rocuronium was 34.9 (11.8) and 35.4 (12.8) seconds in the sevoflurane and control group respectively (p = 0.88). The onset time for deep muscle relaxation was 144.7 (74.7) and 188.6 (124.9) seconds in the sevoflurane and control group respectively. (p = 0.10). Relaxation at 2 min was 92.7 (10.3) % and 89 (13.1) % in sevoflurane and control group respectively. (p = 0.23).

Conclusion: In healthy adults, ventilating the lungs with 2 percent inspired concentration of sevoflurane during routine intravenous induction has no incremental beneficial effect on intubating conditions of 0.6mg kg of rocuronium at 2 minutes.

Keywords: Train of four, Lag time, Accelerometer, Deep muscle relaxation.

INTRODUCTION

It is known that inhalational anaesthetics inhibit the withdrawal reflex at the spinal cord level and have effects on the nicotinic acetylcholine receptor at the neuromuscular junction.[1,2] All in all inhalational agents have some muscle relaxation property.

Innumerable article are present emphasizing the potentiating effect on neuromuscular blockers by volatile anaesthetics.[3-6] These studies have exposed the patient to steady state of inhalational agents for periods inappropriate for routine clinical induction. Study designs resembling routine exposure to inhalational agents, have studied onset and recovery time but not the intubating conditions in patients.[7-9] Intubating conditions of rocuronium with high concentration of sevoflurane have been studied in children, however inhalational induction is not the mode of choice in adults.[10]

We wanted to study whether sevoflurane, in concentrations used routinely during intravenous induction, augments the neuromuscular block of rocuronium enough to have an incremental benefit on intubating conditions. The aim of our study was to evaluate the effect of co- administration of sevoflurane on the intubating conditions of rocuronium, its lag time and onset time for deep relaxation during routine intravenous induction of healthy adults posted for elective surgery. Through this study we endeavour to improve our knowledge of the interaction of the two drugs at induction of anaesthesia.

MATERIAL AND METHODS

It was a prospective randomized controlled trial, conducted after approval from local review board with valid, written, informed consent from patients. Study was carried out at Jaslok hospital and Research centre, Mumbai, over a period of 3 year from April 2004 to November 2006. A thorough pre-anaesthetic evaluation was carried out in all the patients, with airway examination. 60 patients were enrolled in the study. Patients included in the study were of ASA I-II physical status and age 18 to 65 years with Mallampatti classification I and II. Exclusion criteria were patient refusal, patients with neuromuscular disorders, patient on drugs that affect neuromuscular block and pregnant and lactating mothers.For premedication tablet diazepam 5mg was given a night before and at 6am on the day of the surgery with sips of water. 60 patients were randomly divided in sevoflurane and control group of 30 each with toss of a coin. The accelerometer TOF-Watch ^{R} SX (Organon) was used for neuromuscular monitoring. It was attached in the pre-anaesthesia room. The chosen hand was cleaned with spirit over the area around the ulnar nerve and the thumb. Two surface electrodes were applied over the ulnar nerve at the wrist and acceleration transducer was applied to ipsilateral thumb. The temperature probe of the accelerometer was attached on the thenar eminence. In the operation theatre routine standard monitors were attached. Palmer temperature was recorded. 18 G intravenous line was secured and a drip of ringer lactate started. Patients were pre-oxygenated with 100 percent oxygen. Induction in both the groups was with intravenous fentanyl 2 microgram per kg and thiopentone sodium 5mg per kg body weight. The upper limb

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with the neuromuscular monitor was strapped on the arm board. Automatic calibration of TOF watch was performed after the loss of eyelash reflex. Patients in sevoflurane group were ventilated with 2% inspired concentration of sevoflurane in a fresh gas flow of 5l containing 66.66% nitrous oxide and 33.33% oxygen and patients in control group were ventilated with a fresh gas flow of 5l containing 66.66% nitrous oxide and 33.33% oxygen. After stabilization of end tidal carbon dioxide at 30-35 mm Hg, 0.6mg/kg of rocuronium bromide was injected through the running drip in both the groups. The adductor pollicis response to supra maximal stimulation of ulnar nerve was monitored. The parameters recorded were lag time, onset time for deep relaxation, relaxation at 2 mins and intubating condition at 2 minutes after injection of rocuronium. Repeated single twitch mode of stimulation at 1 Hz was started to measure the lag time. Lag time was the time from the injection of rocuronium to first change in single twitch height. The train of four stimulus (2 Hz for 2 seconds at 12 second interval) was then used to record the onset time for deep relaxation. Onset time for deep relaxation was the time from the injection of rocuronium to the disappearance of all four twitches of train of four mode of nerve stimulation. A single experienced anaesthesiologist performed intubation 2 minutes after injection of rocuronium who was not involved in monitoring. TOF ratio was noted at intubation. Relaxation at 2 minutes was measured by TOF ratio. Intubation was judged according to the Copenhagen Consensus Conference scale. Any adverse hemodynamic events were noted. Adverse hemodynamic conditions were defined as a post intubation non invasive systolic and diastolic blood pressure or pulse rate change greater than 30 percent of pre-intubation value.

Based on our pilot studies, the difference in mean onset time for 0.6mg/kg rocuronium with and without sevoflurane was 51 seconds with a standard deviation of 69 seconds in the sevoflurane group. A sample size of 30 in each group was estimated for a probability of 80 percentage (β value=0.2) with 95 percent significance level (α=0.05) to detect a true difference of 51 seconds between the two group.

STATISTICAL ANALYSIS

Qualitative data was assessed by Chi-square test. Analysis of quantitative data between the two groups was done using independent sample t-test. Statistical analysis was done using SPSS version 22

RESULTS

120 patients were assessed for eligibility.60 patients were excluded for age criterion (n=14), for ASA physical status III (n= 18) and Mallampatti class III and IV (n=28). 60 patients were enrolled and analyzed.

The baseline characteristics, ASA physical status and Mallampatti classification are shown in Table 1. Excellent Intubating conditions were seen in 9(30%) patients in sevoflurane group and 6 (20%) patients in the control group. Good intubating conditions were seen in 19(63.3%) patients in both the groups. Poor intubating conditions were seen in 2 (6.7%) patients in sevoflurane group and 5 (16.7%) patients in the control group (Figure 1). The two patients with poor intubating conditions in sevoflurane group had coughing for more than 10 seconds in response to tracheal intubation. Among the five patients with poor intubating conditions in control group, four had coughing for more than 10 seconds in response to tracheal intubation and one patient had coughing and vigorous body movement at intubation. There was no difference in the clinically acceptable intubating conditions, lag time, relaxation at 2 mins and onset for deep relaxation of rocuronium in sevoflurane and control group as shown in Table 2.

Sevoflurane and control group had clinically acceptable intubating conditions of the trachea in 28 (93.3%) and 25 (83.3%) patients respectively (p = 0.42). The lag time of 0.6 mg/kg of rocuronium was 34.9 (11.8) and 35.4 (12.8) seconds in the sevoflurane and control group respectively (p=0.88). The onset time for deep muscle relaxation of 0.6 mg/kg of rocuronium was 144.7 (74.7) and 188.6(124.9) seconds in the sevoflurane and control group respectively (p = 0.10). Relaxation at 2 min was 92.7 (10.3) % and 89 (13.1) % in sevoflurane and control group respectively (p = 0.23). The palmar temperature in both the groups had no statistically significant difference. The palmar temperature in sevoflurane was 28 (0.15) ^{0}C and in the control group was 27.9 (0.19) ^{0}C (p = 0.88). In sevoflurane group two patients had fall in diastolic blood pressure of more than 30% post intubation and one patient had a rise in diastolic blood pressure more than 30% from pre intubation values. In control group two patients had rise in diastolic pressure of more than 30% from pre intubation value.

DISCUSSION

We had hypothesized that a decrease in onset time of rocuronium or an improvement in intubating conditions after co-administering of sevoflurane along with intravenous anaesthetics may be observed. We chose to use clinically appropriate doses of both the drugs which is two times ED^{95} (0.6mg/kg) of rocuronium and approximate one MAC of sevoflurane (2% inspired concentration). Though the onset time for deep relaxation of rocuronium was lesser in the sevoflurane group and patients in sevoflurane group had more excellent and less poor intubating conditions of the trachea, none of our parameters showed any statistical significant difference. The lack of difference can be explained by analyzing the mechanisms of potentiation NMB of by inhalational agents. The proposed mechanisms are inhibition of spinal motor neuron, inhibition of post synaptic nicotinic acetyl choline receptor or general enhancement of antagonist affinity at receptor site by inhalational agents.[11,2,12-14] The degree of potentiation of neuromuscular block by volatile anaesthetics depends on their aqueous concentrations. Time for half-equilibration of sevoflurane in muscle group is 70-80 minutes.[15] Low potency neuromuscular blockers like rocuronium have more molecules to equilibrate between central compartment and effect site, thus have faster onset of action. During routine intravenous induction with co-administration of sevoflurane the exposure time is not enough for sevoflurane to equilibrate in muscle compartment. Thus incremental benefit of sevoflurane for intubating conditions were not seen. Our study observed similar results

Some recent studies have concluded earlier acceptable intubating conditions with sevoflurane under similar anaesthetic conditions in adult.[16] The dose used is more than 2 times ED^{95}. In this study calibration of TOF watch was after sevoflurane stabilization. The maximum twitch height achieved in the sevoflurane group

may be lesser than that achieved in the non sevoflurane group and thus the time for onset of maximum depression is less than control.

The dose and time for intubation has been kept constant in our study design which makes the two groups comparable. As in our study lack of effect of sevoflurane on lag time and onset time of 0.6mg-kg has been reported by other studies.[8,17]

Acceptable Intubating conditions with low dose of rocuronium have been found with higher concentration of sevoflurane in children.[10] There are no controls in these studies. The potentiation seen may be due to the depth of anaesthesia. Acceptable intubating conditions with low dose of rocuronium and intravenous anaesthetics have also been reported.[18] The authors, from the analysis of results of present and other studies, propose keeping depth of anaesthesia constant when studying the effects of general anaesthetics on neuromuscular blockers.

The drawback of our study was an inability to measure end tidal concentration of sevoflurane due to lack of resources and the study was not blinded. The low blood gas solubility of sevoflurane, presence of 66.66 percent nitrous oxide and a fresh gas flow of 5 l was expected to provide early equilibration of sevoflurane in the central nervous system. The time to half-equilibration in the vessel rich central nervous system is about 2 minutes for sevoflurane.[15]

The onset time in our study is the time for deep relaxation when the TOF count is zero. This is a plane of neuromuscular block when supplemental doses of neuromuscular blockers are not required. We wanted to compare the time to achieve this plane of NMB.

The Copenhagen consensus conference standard suggests maintaining core temperature of 36°C and surface temperature of 32°C for good clinical research practice in neuromuscular monitoring.[19-21] No active means of raising temperature of the limb monitored was used to mimic routine practice. Routinely warmers are started after induction and positioning.[22] The absolute value of lag time and onset time in our study should be compared keeping the temperature and mode of stimulation in mind.

CONCLUSION

Thus it is seen in our study that in healthy adults, ventilating the lungs with 2 percent inspired concentration of sevoflurane during routine intravenous induction has no incremental beneficial effect on intubating conditions of 0.6mg/kg of rocuronium at 2 minutes.

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Appendix

Copenhagen Consensus Conference scale

	Excellent	**Good**	**Poor**
Laryngoscopy	Easy	Fair	Difficult
Vocal cord(position)	Abducted	Intermediate	Closing
Vocal cord(movement)	None	Moving	Closed
Movement at intubation(body)	None	Slight	Vigorous
Movement at intubation(coughing)	None	Diaphragm	>10 seconds

Copenhagen Consensus Conference scale: Excellent (all excellent conditions), Good (all excellent/good conditions), Poor (any one poor condition). Excellent/Good scale are clinically acceptable. Poor scale is clinically not acceptable.