Original Article

Indian Journal of Anaesthesia and Analgesia
Volume 4 Number 2, April - June 2017 (Part–1)
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.4217.11

Effect of Etomidate and Propofol on the Onset of Neuromuscular Blockade a Randomized Prospective Comparative Study

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Abstract

Introduction: The onset time of neuromuscular blockade can be influenced by factors such as hypnotics which interfere with muscle blood flow and muscle relaxation induced by nondepolarizing neuro-muscular blockers. *Aim:* This study was designed to test whether etomidate, with its favourable haemodynamic characteristics, is associated with a shorter onset time of neuromuscular block or propofol with its action on the neuromuscular junction is associated with faster onset of neuromuscular block. *Settings and Design:* A prospective randomised comparative study. *Methods and Material:* 60 patients scheduled for elective surgery were randomly allocated into 2 groups to receive 0.4mg/kg of etomidate or 2mg/kg of propofol, vecuronium 0.1 mg/kg was administered and ulnar nerve was stimulated supramaximally and train of four responses was recorded with kinemyography. Time to 100% neuromuscular block, NIBP and HR were measured. *Results:* The onset time was faster in etomidate group compared to propofol but it was not statistically significant. There was a negative correlation between onset time and the maximum percent change in mean arterial pressure. *Conclusions:* Propofol and etomidate had a similar behaviour regarding time for vecuronium-induced neuromuscular block. The onset time of the vecuronium induced neuromuscular block depends not only on the circulatory factors but also on the noncirculatory factors too.

Keywords: Etomidate; Propofol; Vecuronium; Onset Time of Neuromuscular Block.

Introduction

The onset time of neuromuscular blocking agents is one of the most broadly studied and reported pharmacodynamic variables in anaesthesia, because of the relative ease in objectively assessing it with neuromuscular monitoring devices and also due to large number of possible dosing permutations in which these drug can be administered.

Few hypnotics have certain properties and mechanisms, which may interfere with muscle relaxation induced by nondepolarizing neuromuscular blockers (NDNMB) [1]. The onset time of neuro muscular blockade by the relaxants will be affected by the changes in the regional blood flow [2] and rate at which a pharmacologically effective concentration is achieved in the biophase, in this case the neuromuscular junctional cleft [3]. This is influenced by the dose of drug, its pharmacokinetic profile, and also the speed of injection (bolus effect) [4].

Etomidate with its safe cardiovascular risk profile is less likely to cause a significant drop in blood pressure in comparison with other induction agents [5]. Propofol enables endotracheal intubation with its action on neuro muscular junction and by decreasing the reactivity of larynx and pharynx muscle tone without neuromuscular blockers [6].

This study is designed to test whether etomidate, with its favourable haemodynamic characteristics, is associated with a shorter onset time of neuromuscular block or propofol with its action on the neuromuscular junction is associated with faster onset of neuromuscular block. The need for the study is to relate these data to the relative speed and ease by which we can pass tracheal tube

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Received on 23.01.2017
Accepted on 28.01.2017

during rapid sequence induction or during a potentially difficult intubation.

Methodology

Randomized clinical trials were conducted after approval from institution ethics committee and written informed consent from patients. The study included patients, aged 18-60 years physical status ASA I-II, scheduled for elective surgery under general anaesthesia with tracheal intubation and mechanical ventilation. Randomization was based on sealed envelope technique.

We excluded patients suffering from cardio-vascular or neuromuscular disorders, renal or hepatic diseases or taking medications which might interfere with normal cardiovascular physiology or neuromuscular transmission and those with indicative signs of difficulty to perform the laryngoscopic and tracheal intubation manoeuvres (Mallampati III and IV). Sample size calculation was based on onset time of neuromuscular block from previous studies by Gill and Scott [1] considering a 0.05 level of significance and 80% power with expected difference of 6%. The required size was calculated at n=60 (30 in each group).

60 patients scheduled for elective surgery were randomly allocated into two groups of 30 each to receive 0.4 mg/kg etomidate (group E) or 2mg/kg propofol (group P). Patient's basal parameters-Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) and Electrocardiography were monitored using-pulse oximetry, Non Invasive Blood Pressure (NIBP), and ECG monitor respectively. Datex kinemyograph was used at the adductor pollicis to monitor and record the twitch response to the train of four (TOF) stimulation. MAP and HR were used as indirect indicators of muscle perfusion.

All the patients were premedicated with midazolam 1mg. Patients in both the group will receive 2 mcg/kg fentanyl followed by preoxygenation for 4 minutes by face mask. After preoxygenation, patients in E group received 0.4 mg/kg etomidate and patients in P group received 2 mg/kg propofol. Neuromuscular monitoring was initiated after obtaining the control values by supramaximal stimulus square wave stimuli applied to the ulnar nerve at 2 Hz with pulse width 0.3 ms repeated every 15s. After baseline calibration of this device vecuronium bromide 0.1mg/kg was given over 5 seconds. During this time anaesthesia was maintained with 100% Oxygen. Onset time was noted (the interval from the end of muscle relaxant bolus injection until the maximal suppression of T1%). MAP and HR were measured non-invasively and recorded every 1 min until 100% depression of the first twitch of the train of four.

The results were analysed with the SPSS version 20 statistical package using independent student t test to calculate the differences between the two groups. Correlation analysis was used to evaluate potential relationships between the MAP and the onset time. Statistical level of significance was set at $p< 0.05$.

Results

There were no significant differences in demographic profile between the two groups (Table 1).

Maximum changes in MAP and HR that occurred between induction and maximal block (100% depression of the first twitch of the train-of-four) were calculated as percentage of baseline value.

The onset time was faster in etomidate group

Table 1: Patient data [mean (range or SD)]

	Group E	Group P
Age (yrs)	31.27 (18-55)	31.07 (14-64)
Weight (kgs)	57.7 (2.20)	57.57 (2.26)

Table 2: Onset time, maximum percent change in heart rate (HR) and mean arterial pressure (MAP) (mean (SD) [range])

	Group E	Group P	P value
Onset time (S)	193.70(11.61)	217.40(11.41)	0.134
HR	5.59(3.93)	2.16(3.43)	0.142
Max % Change	[-56.25-26.25]	[-57.41-34.58]	
MAP	12.56(3.69)	17.78(2.86)	0.267
Max % Change	[-55.22-57.14]	[-15.49-58.45]	

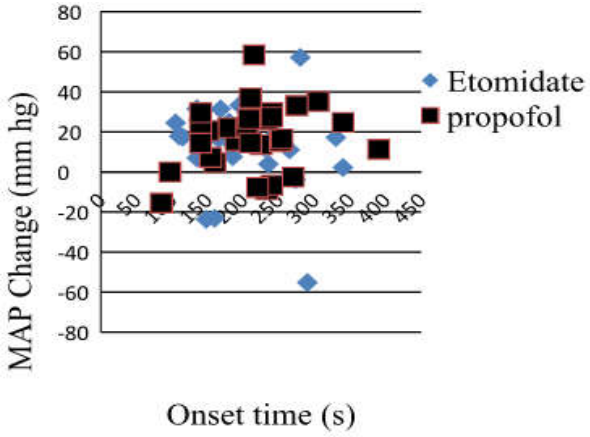

Fig. 1: Correlation between onset time and maximum percent change in MAP
r= -0.102; P Value= 0.436

(193.70±11.61s) compared to propofol (217.40±11.41s) but it was not statistically significant. There was no significant difference in the maximum percent change in MAP and HR between two groups (Table 2).

There was a negative correlation between onset time and the maximum percent change in MAP (Figure 1).

Discussion

The precise measurement of onset time is essential to estimate the timing of tracheal intubation. The onset time of the neuro muscular block is determined by the blood flow and the circulation time to the target organ. For example, onset time is faster when a neuromuscular blocking drug is injected directly into the pulmonary artery rather than into a peripheral vein [7]. Accordingly, neuromuscular block is specifically rapid in highly perfused muscles and resultant onset of neuromuscular block may be affected by the intravenous anaesthetics during anaesthetic induction [8].

This study is needed to evaluate the onset of action of neuromuscular blockade with non-depolarizing muscle relaxant, using propofol or etomidate as hypnotic agents during anaesthesia induction. Vecuronium was chosen as the neuromuscular blocking drug as it has been shown to have virtually no cardiovascular effects. Nitrous oxide and volatile agents were given when the study was complete to minimize changes in haemodynamic variables in order to highlight the effect of the induction agent on the cardiovascular system.

Gill and Scott related the differences in onset time of neuromuscular block observed with vecuronium to better maintenance of haemodynamic variables associated with etomidate compared to thiopental and propofol [1]. Furthermore etomidate itself potentiates the neuromuscular blocking activity of a nondepolarizing neuromuscular blocking drug. Braga afa et al [6] concluded that, the neuromuscular block with cisatracurium was faster, with better tracheal intubating conditions in patients receiving propofol compared to those receiving etomidate which was attributed to action of propofol on neuromuscular junction in reducing the channel opening time of the muscle nicotinic receptors. In our study the onset time was faster in etomidate group compared to propofol but it was not statistically significant. The results of our study differ from results by Gill and Scott [1] and Braga afa et al [6].

The onset time of neuromuscular blockade depends not only on the circulatory factors but also on the non-circulatory factors [9]. In our study there was a weak correlation between the onset time and the MAP signifying a partial contribution of the circulatory factors to the onset time. Ryu Komatsu showed no correlation between cardiac index and onset of the blockade and that the onset of the vecuronium-induced neuromuscular block is primarily determined by factors other than cardiac output [10]. Audibert and Donati showed that tourniquet inflation during the onset of neuromuscular block slowed the onset of block with rocuronium, but not with mivacurium or vecuronium [11]. They reported that the onset time of drugs with rapid onset, such as rocuronium, chiefly depends on the circulation time to muscle, whereas the onset of action of vecuronium and mivacurium depends on the process of redistribution of drug from an extrajunctional to a junctional area.

The neuro muscular blockade time is influenced by the factors which interfere with neuro muscular monitoring [9,12]. Studies have shown that the onset of action of NDNMB has an inverse relation to the times for muscle response stabilization and stimulus frequency [9,13-14]. The probable explanation is that the series of contractions induced by nerve stimulation for a prolonged time increases muscle blood ûow and results in higher drug amount in the stimulated muscle. Alternate explanation is that there is neurotransmitter depletion at the stimulation site due to the high frequency stimulation, with resultant shortening of latency and greater degree of neuromuscular block [15,16].

Our study design has some limitations. First, most of the drugs for anaesthesia (midazolam, fentanyl)

may have influenced the patient's hemodynamics and the onset time of neuromuscular blocking agents, thus possibly having a certain effect on our results. Second we used non invasive monitoring of blood pressures. Invasive monitoring would have given accurate hemodynamic values and thirdly cardiac output monitoring would have been a better indicator of muscle perfusion.

In conclusion, propofol and etomidate had a similar behaviour regarding time for vecuronium-induced neuromuscular block. The onset time of the vecuronium induced neuromuscular block depends not only on the circulatory factors but also on the noncirculatory factors. The combination of etomidate or propofol with vecuronium cannot be substituted for rapidly acting non depolarising muscle relaxants.

Conflict of interests: None

Key Message

The combination of etomidate or propofol with vecuronium cannot be substituted for rapidly acting non depolarising muscle relaxant.

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