The Role of Bolus Injection of Saline with Arm Elevation on Rocuronium onset Time: A Randomized Control Study

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Abstract

Background: The onset time of neuromuscular blockade is a crucial time associated with the risk of hypoxia and pulmonary aspiration. Various strategies have been undertaken to shorten this onset time. Therefore, we investigated the effects of bolus of 20 ml saline followed by limb elevation after administration of rocuronium in a dose of 0.6 mg/kg to study the onset time. Methodology: Thirty patients were randomly allocated to the bolus saline group or control group. General anesthesia was induced and maintained with fentanyl and propofol. Rocuronium 0.6 mg/kg intravenous (IV) was administered followed by 20 ml saline bolus and limb elevation in the study group compared to administration of 0.6 mg/kg in a running drip only in the control. Onset of neuromuscular block was assessed by acceleromyography at the adductor pollicis muscle with train-of-four stimulation. Results: The lag time was shorter in bolus group (34 s median) than in control group (45 s median), \( P < 0.017 \). The onset time was shorter in bolus group (55 s median) than in control group (110 s median), \( P < 0.001 \). The T1 recovery to 25% was longer in bolus group (42 min median) than in control group (39 min median) which was statistically not significant. Conclusion: Rocuronium 0.6 mg/kg IV followed by bolus 20 ml saline and concomitant limb elevation resulted in shorter lag time, faster onset of neuromuscular blockade, good intubating conditions without prolonging clinical duration of action when compared to the control.

Keywords: Arm elevation, bolus injection, rocuronium

Introduction

The onset of neuromuscular blockade is a stage of anesthesia during which the patient is exposed to risk of hypoxia and pulmonary aspiration. Various strategies have been developed to shorten the onset time of muscle relaxation, including increasing the dose, timing technique, and priming technique. However, these alternatives often provoke a long duration of muscle paralysis or muscle weakness before induction of anesthesia. Although succinylcholine is known for its rapid onset, it has numerous side effects making its use contraindicated in certain situations. Rocuronium with relatively fast onset is a suitable alternative to succinylcholine for neuromuscular blockade during rapid sequence induction. Rocuronium in a dose of 0.9–1.2 mg/kg intravenous (IV) can shorten the onset time and prolong the duration of action. Hence, to accelerate the onset time of rocuronium without prolonging the neuromuscular blockade, various pharmacological or nonpharmacological techniques have been used in clinical practice, but the conclusions are still inconsistent. The onset time of neuromuscular blockers is dependent on factors such as circulation time and muscle blood flow. This onset time is affected by the time taken for the drug from peripheral IV catheter to reach the central circulation. IV drug administration through a peripheral vein is typically followed by administration of a fluid bolus in many clinical practices. Briefly elevating the extremity during and after drug administration theoretically may also recruit the benefit of gravity to facilitate delivery to the central circulation but has not been systematically studied.

Techniques that are used to shorten the onset time of neuromuscular-blocking drugs such as priming and timing principle have various side effects, and the use of these techniques has decreased.

During resuscitation, drug administration through peripheral venous access is followed by 20 ml of IV fluid bolus and...
brief extremity elevation such that gravity aids faster delivery of the drug into the central circulation. There is limited evidence with two studies in which 20 ml saline flush immediately after administration of neuromuscular blockers followed by limb elevation which shortened the lag time and onset time in the study group compared to control group. One of the earliest reports conclude that administration of vecuronium into a pulmonary artery significantly shortened the onset time by approximately 40 s than when compared to administration into a dorsal vein of the hand.

Therefore, in this prospective study, we tested the hypothesis whether the bolus injection of 20 ml saline bolus after rocuronium in a dose of 0.6 mg/kg with concomitant limb elevation shortened the onset of action when compared with the control comprising of the same dose of rocuronium without fluid bolus and limb elevation. In addition, we also assessed time for 25% recovery between two groups and tracheal intubating conditions.

**Methodology**

This randomized double-blind controlled study was initiated after approval of departmental dissertation committee and Institutional Ethics Committee.

**Sample size**

A sample size of 12 patients per group was needed to detect a 30 s difference in the onset time at a 5% significance level with a power of 80% ($\alpha = 0.05, \beta = 0.2$). Therefore, 30 consenting patients in the age group of 18–65 years with American Society of Anesthesiologists (ASA) Grade I and II and body mass index (BMI) in the range of 18.5–29.9 kg/m$^2$ requiring general anaesthesia for elective surgical procedure and providing written informed consent were included in the study. Patients with anticipated difficult airway, risk of aspiration, neuromuscular disease, and who were taking any medications that might interfere with neuromuscular transmission were excluded from the study.

**Observers**

**Observer 1**

An anesthesiologist evaluated the patient preoperatively, obtained the written informed consent, and he performed the IV induction followed by administration of rocuronium as per the allocated group.

**Observer 2**

An anesthesiologist (blinded to the study group) recorded the lag time, onset time, and 25% recovery of T1.

**Observer 3**

An experienced anesthesiologist unaware of the two groups in the study performed the endotracheal intubation and assessed the intubating conditions recovery to 25%.

The patients were evaluated preoperatively; a written informed consent was obtained on the day before surgery. All patients received fasting orders as 2 h for clear fluids and 6 h for solids and were premedicated orally with tablet alprazolam 0.25 mg, tablet metoclopramide 10 mg, and tablet ranitidine 150 mg on the night before surgery.

Patients were randomly assigned to the bolus saline group (B group) or the control group (C group) using a computer-generated randomization table. Concealment was ensured using sequentially numbered, opaque sealed envelope.

**Bolus group**

Rocuronium 0.6 mg/kg administration was followed by injection of 20 ml saline over 5 s into the IV line while maintaining the arm elevated vertically for 10 s.

**Control group**

Rocuronium 0.6 mg/kg was given over 5 s into a rapidly running infusion through a T-port in the IV line.

Blinding was ensured by placing a screen between observer 1 and 2 and turning back toward the screen. The third observer was involved following the administration of study drug to ensure blinding.

**Anesthetic management**

On arrival in the operating room, pulse oximetry, electrocardiography, and noninvasive arterial blood pressure monitoring were established. An 18-G peripheral IV cannula was secured in the right dorsal hand vein. After obtaining the baseline value of the parameters, patients were preoxygenated with 100% $O_2$ for 3 min. Induction of general anesthesia was done with IV propofol 1.5–2 mg/kg and IV fentanyl 1–2 $\mu$g/kg body weight. Once the patient was induced, ability to mask ventilate was confirmed. Mask ventilation was continued with $O_2$ and isoflurane to achieve Minimum Alveolar Concentration (MAC) of 1–1.2. All the individuals were administered rocuronium with/without the additional maneuvers for the study group as mentioned above.

**Neuromuscular monitoring**

Neuromuscular block monitoring was started by observer 2 immediately after the induction of anesthesia by using accelerometry (train-of-four [TOF] guard) at adductor pollicis of the arm contralateral to IV cannulation. Ulnar nerve of the arm contralateral to the IV cannula was stimulated supramaximally through surface electrodes according to the guidelines for Good Clinical Research Practice in pharmacodynamics studies. TOF guard programmed to deliver impulses at 2 Hz with a single square wave pulse of 0.2 ms in duration for 1.5 s repeated every 12 s at 30 mA was applied. Adductor pollicis contractions were measured with a piezoelectric accelerometer fastened to the volar aspect of thumb. The arm temperature was monitored using a surface probe and kept at or above 32°C using a heating blanket. Once the patient was unresponsive with the absence of eyelash reflex, the acceleromyograph was calibrated for supramaximal TOF stimulation. The degree of neuromuscular block was measured as decrease in contractile response of the first response (T1) relative to control.
The following observations were made in the study in both the groups

Lag time was defined as the time from the administration of rocuronium injection until the first decrease in T1 of TOF ≥5%.

Onset time was defined as the time from administration of rocuronium until T1 block reached ≥95%.

Tracheal intubating conditions were judged by an experienced anesthesiologist (observer 3) unaware of the two groups in the study as described by Krieg et al.[10] and shown in Table 1.

Total score of intubation conditions is categorized as excellent, good, fair, and poor. Score of 6–9 was taken as acceptable and zero to five was taken as unacceptable.

After tracheal intubation, mechanical ventilation was resumed to maintain an end-tidal carbon dioxide tension of 30–35 mmHg. IV fentanyl was given intermittently, at the discretion of the anesthetist. The time to recovery of T1 to 25% of baseline (clinical duration of action) was recorded in both the two groups, and at this point, the study was concluded. Thus, a team of three anesthesiologists could implement the study as per the protocol and were able to test the efficacy of this simple noninvasive technique.

Data analysis

Statistical analysis was done using SPSS version 16.0 (SPSS Inc, Chicago, USA) for Windows. Parametric data (age, BMI) were analyzed using independent samples t-test, and nonparametric data were analyzed using Mann–Whitney U-test.

The Hodges–Lehmann method was used to estimate the median of the difference between the groups with a 95.2% confidence interval (CI). \( P < 0.05 \) was considered statistically significant.

Results

A total of 30 patients undergoing elective surgery aged 18–65 years under general anesthesia were randomly allocated into two groups, namely, Group B – bolus saline and Group C – control.

The two groups were comparable with respect to age, gender, BMI, and ASA as shown in Table 2.

Neuromuscular measurements for the bolus and control groups are expressed as median (interquartile range). Estimated difference between the groups using Hodges–Lehmann method is expressed as median (95.2% CI). Negative or positive value of the estimated difference indicates that the saline flush shortened or lengthened the neuromuscular measurement, respectively.

The lag time and onset time were shorter in bolus group than in control group and were statistically significant as shown in Table 3. A pictorial representation of comparison of lag time, onset time and tracheal intubating conditions is shown in Figure 1. Although the \( T_1 \) recovery to 25% was longer in...
bolus group than in control group, it was not statistically significant.

There was no statistically significant difference between the two groups with respect to total score of intubating conditions as shown in Table 4.

Box-and-whisker plots for the lag time, onset time, and for T1 recovery to 25% show the median (central line inside the box) and interquartile ranges (end of the whiskers).

DISCUSSION

We found that a 20 ml saline flush with concomitant arm elevation immediately after administration of rocuronium 0.6 mg/kg shortened the lag time to 34 s and the onset time to 55 s when compared to 45 s and 110 s in control group. However, saline flush with arm elevation did not prolong the clinical duration of action of rocuronium.

Several studies in the past have investigated to reduce the transit time of neuromuscular blockers from the peripheral injection site to the effect site. IV drug administration through a peripheral vein is typically followed by administration of a fluid bolus in many clinical practices.

A study conducted by Ishigaki et al.[6] among 48 patients on the effect of 20 ml saline flush immediately after vecuronium 0.6 mg/kg administration reported that the lag time and onset time were shortened to 39 ± 11 s and 73 ± 21 s in the study group compared to 46 ± 10 s and 87 ± 22 s in the control along with prolongation of the recovery phase of neuromuscular blockade. Nitahara et al.[7] studied the effect of bolus injection of 20 ml saline with arm elevation on the onset time of vecuronium 0.1 mg/kg administered through a peripheral vein and found that bolus saline injection resulted in a shortened lag time of 47.2 s and 67.9 s in control with a mean onset time of neuromuscular block of 104.6 s in bolus saline versus 128.3 s in the control. In consensus with above-mentioned studies, we also observed that the onset time was shortened by bolus injection and arm elevation.

American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care mentioned that if a resuscitation drug is administered by a peripheral venous route, it should be followed by a bolus of 20 ml IV fluid to facilitate the drug flow from the extremity into the central circulation.[9]

Iwasaki et al.[8] reported that the administration of vecuronium through a pulmonary artery catheter into the right atrium shortened the latent onset time by 11 s compared with 82 s when vecuronium was administered into the dorsal vein of the hand. Thus, it was concluded that drug administration followed by a 20-ml saline flush may be comparable with drug administration into the right atrium. They showed that there was a significant correlation between the cardiac index and the onset time of neuromuscular block by vecuronium.

Another explanation given by Nitahara et al.[7] is that the more rapid onset time of rocuronium in the bolus saline group may be due to the increase in preload and hence cardiac output. There is a possibility that the hemodynamic changes can affect the pharmacokinetics associated with the onset of neuromuscular blockade. However, the effect of cardiac output on the onset time of neuromuscular-blocking drugs remains unclear as it is not the only determining factor. However, in a study done by Komatsu et al., increased cardiac output caused by bolus ephedrine failed to reduce the onset time of vecuronium.[21] As hemodynamic effects and cardiac output were not measured in our study, we are unable to derive conclusions on the possible change in cardiac output after bolus injection of 20 ml saline. The difference in the rocuronium infusion rate does not change the transit time, whereas saline flush decreases the transit time of rocuronium. It is unlikely that a 20-ml saline flush itself changes cardiac output and muscle perfusion. Because the 20-ml saline flush also pushed propofol and fentanyl from the peripheral vein of the upper extremity, these drugs might have reduced cardiac output, resulting in the longer transit time in the saline flush group.

A study conducted by De Haes et al.[11] showed that the rate of rocuronium injection when administered through a running fluid infusion significantly decreases time to 50% relaxation, but not time to 90% relaxation. The influence of the administration scheme on the circulation time may underlie this discrepancy in results.

The time to 25% recovery of T1 in our study was slightly longer in the bolus saline group (42 min) than in the control group (39 min), but this difference was not significant. In contrast to our results, some studies mentioned bolus injection causing higher peak concentration of drug, and hence, recovery phase can be prolonged.[11] A study conducted in dogs during cardiac arrest concluded that bolus injection of 20 ml saline after dye administration resulted in enhanced dye circulation time and a higher peak levels.[12] A higher peak plasma concentration at the effect site can prolong the recovery phase. Therefore, saline bolus injection after rocuronium might cause a higher peak plasma level and greater drug delivery to the muscles.

The method used in this study requires no special apparatus. The bolus can be drawn from the same IV fluid infusion with a 20-ml syringe; therefore, the syringe is the equipment necessary to shorten the onset time of rocuronium with no additional personnel required.

We used accelerometry (TOF guard) for neuromuscular monitoring. The guidelines for good clinical research practice in pharmacodynamic studies of neuromuscular-blocking agents recommend a 10-s interval for 0.1-Hz single twitch stimulation and a ≥12-s interval for TOF stimulation. We used TOF stimulation to measure the lag time, onset time, and T1 to 25% recovery using the TOF ratio at 12 s interval.[7]

We have attempted to reduce observer bias by blinding the anesthesiologist who recorded the time course of rocuronium-induced block.

The bore size of the cannula may also influence the latent onset time and onset time because a smaller bore cannula may result...
in high-speed spouting of the rocuronium solution. In addition, we have standardized the IV bore size of 18G, site being on the dorsal aspect of hand in both the groups.

Limitations
This study only evaluated the pharmacodynamic effect of rocuronium bromide; further research is necessary to study the influence of rocuronium concentration on recovery phase. The ideal volume of chaser solution is unclear, and there is scope to study the onset time with higher volumes of the bolus injection. Cardiac output and systemic vascular resistance were not measured in our study; as a result, it was not possible to draw conclusions on a possible change in cardiac output after bolus injection of 20 ml saline with arm elevation.

Conclusion
Our study comparing IV injection of 0.6 mg/kg of rocuronium into a running drip versus bolus injection of 20 ml saline with concomitant arm elevation following IV rocuronium 0.6 mg/kg resulted in shorter lag time, faster onset of neuromuscular blockade, and good intubating conditions early without prolonging clinical duration of action. We suggest that bolus saline with arm elevation caused more rapid drug delivery to the central circulation and hence shortened the onset time.

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Conflicts of interest
There are no conflicts of interest.

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