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Rocuronium Infusion to Maintain a Deep Block without Inducing an Intense Block

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ABSTRACT

Background : Deep neuromuscular blockade has been demonstrated to enhance surgical conditions. The present study investigated the appropriate infusion rate of rocuronium and its adjustment method for maintaining a deep level of neuromuscular blockade without inducing an excessively intense block.

Methods : The participants were 10 adult patients anesthetized with propofol. Neuromuscular blockade was evaluated with acceleromyography at the adductor pollicis. Rocuronium infusion began with a 0.6-mg/kg bolus. Continuous administration started once the response to posttetanic count stimulation returned, and the infusion rate was adjusted to maintain a posttetanic count of 1 to 5 without inducing a posttetanic count of 0. Changes in the rocuronium infusion rate were analyzed.

Results : The mean infusion rates of rocuronium after the initial bolus were 13.2 μg/kg/min at 90 minutes, 12.1 μg/kg/min at 120 minutes, and 10.8 μg/kg/min at 150 minutes. The infusion rate of rocuronium decreased significantly over time. None of the patients experienced an intense block after the start of continuous rocuronium administration.

Conclusion : The average infusion rate required to maintain a deep block was 13.2 μg/kg/min, assessed 90 minutes after the initial bolus. Subsequently, a gradual reduction in the rocuronium infusion rate was essential to prevent an overly intense block.

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Key words : rocuronium, deep neuromuscular blockade, continuous infusion, tapering

INTRODUCTION

Neuromuscular blocking agents (NMBAs) are commonly used to facilitate endotracheal intubation, immobilize patients, and enhance surgical conditions under general anesthesia[1]. Although neuromuscular blockade is beneficial during surgery, ensuring complete recovery after surgery is crucial to prevent pulmonary complications[2]. Recently, the American Society of Anesthesiologists and the European Society of Anaesthesiology and Intensive Care issued guidelines for the use of NMBAs in the perioperative period[1,3]. These guidelines recommend using sugammadex to reverse the effects of shallow, moderate, and deep neuromuscular blocks induced by the NMBA rocuronium. Sugammadex has a high affinity for rocuronium and also enables effective and rapid recovery from deep levels of neuromuscular blockade[4,5]. The optimal dose of sugammadex is determined according to the level of neuromuscular blockade. Recommended doses are 2 mg/kg for shallow and moderate blocks, a train-of-four (TOF) count of 2 to a TOF ratio less

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than 0.9, and a higher dose of 4 mg/kg for a deep block, posttetanic count (PTC) of 1 to a TOF count of 1[1]. However, a sugammadex dose has not been recommended in cases of intense block with no response to any nerve stimulation pattern. Therefore, a safer way of managing general anesthesia would be to avoid an intense neuromuscular blockade during surgery.

To prevent unstable neuromuscular blocks during surgery, an effective dosing method is the continuous infusion of NMBAs. On the other hand, care must be taken to avoid excessive effects if rocuronium, which is an intermediate-acting NMBA, is administered in continuously large quantities. The continuous infusion of rocuronium does not require the administration rate to be reduced to maintain a moderate block[6]. However, a previous study described the average continuous infusion rate required to maintain a deep neuromuscular block but did not mention the rate being adjusted during general anesthesia[7].

Hence, this study aimed to investigate the appropriate infusion rate of rocuronium and its adjustment method to maintain a deep level of neuromuscular blockade without inducing an excessively intense block.

MATERIALS AND METHODS

1. *Study recruitment*

This study was performed at The Jikei University Hospital (Tokyo, Japan) from June 2016 through March 2023. It was approved by the Ethics Committee of The Jikei University School of Medicine for Biomedical Research 27-269 (8,154) and was conducted in adherence with the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

Enrolled as participants were patients aged 20 to 65 years who had been classified with an American Society of Anesthesiologists physical status of 1 to 2 and scheduled to undergo elective surgery requiring NMBAs and general anesthesia for 1.5 to 5 hours. Patients were excluded if they met any of the following criteria : American Society of Anesthesiologists physical status ≥ 3, pregnancy, body mass index < 18.5 kg/m^2 or > 30 kg/m^2, renal dysfunction (serum creatinine levels > 1.1 mg/dL in men and > 0.8 mg/dL in women), hepatic dysfunction (serum transaminase levels > 100 U/L), metabolic disorder, neuromuscular disorder, dyspnea requiring oxygen administration, symptomatic airway stenosis, bronchial asthma, hypersensitivity to rocuronium or sugammadex, atopic disease, history of anaphylaxis, taking antihistamine drugs or antiallergy drugs or both for > 1 month, taking drugs on the day of surgery which can interact with NMBAs (e.g., calcium antagonists, anticonvulsant agents, aminoglycoside antibiotics, polypeptide antibiotics, and metronidazole), requiring management with hypothermia during surgery, difficulty with appropriate neuromuscular monitoring, emergency surgery, and life-threatening medical conditions. Before being enrolled, all patients were required to provide written informed consent.

2. *Study protocol*

During surgery all patients were monitored with electrocardiography, noninvasive blood pressure measurement, and pulse oximetry. Anesthesia was induced and maintained with propofol, fentanyl, remifentanil, and rocuronium. Propofol was infused with a target-controlled infusion system (Diprifusor® ; AstraZeneca, Cambridge, United Kingdom) to maintain a bispectral index of 40 to 60 throughout surgery. Neuromuscular function was evaluated at the adductor pollicis with acceleromyography (TOF-Watch® SX ; Merck & Co., Inc., Rahway, NJ, USA), with assessments based on the TOF ratio, TOF count, and PTC. The TOF ratio is determined by comparing the response to the 4th twitch to that of the 1st twitch in a series of 4 consecutive stimuli. The TOF count refers to the number of responses to 4 consecutive stimuli. The PTC represents the number of responses to single twitches following high-frequency tetanic stimulus. Rocuronium was administered as a bolus of 0.6 mg/kg, and the trachea was intubated 30 seconds after a TOF count of 0 had been confirmed. After a return of response to PTC stimulation was observed, continuous administration of rocuronium was started at a rate of 7 μg/kg/min by following the instructions in the manufacturer's package insert. The PTC was measured with intervals > 6 minutes[8], and the infusion rate of rocuronium was adjusted to maintain neuromuscular blockade at a PTC of 1 to 5. When the surgical procedure had been completed, infusion of rocuronium was stopped and 4 mg/kg sugammadex was administered after a PTC ≥ 1 had been confirmed. Neuromuscular monitoring was continued until the TOF ratio recovered to ≥ 0.9.

3. Statistical and data analyses

The study population was characterized via descriptive statistics. The adjustment period was 90 minutes after the initial bolus of rocuronium. The normality of the data was assessed with the Shapiro–Wilk test and Q–Q plots. To analyze changes in the mean infusion rates of rocuronium across the time points of 90, 120, and 150 minutes after the initial bolus of rocuronium, mixed-effects analysis with the Holm–Šídák multiple comparisons test was used. Statistical analyses were conducted with GraphPad Prism 9.5 (GraphPad Software, San Diego, CA, USA) with two-tailed hypothesis testing. Data are presented as mean (SD) for normally distributed variables, and $p < 0.05$ was considered significant for all analyses.

Table 1. Patient characteristics

Characteristic	Number of patients (n = 10)
Age, years, mean (SD)	38 (8)
Sex	
Male	6
Female	4
ASA physical status classification	
1	7
2	3
Body mass index, kg/m^2, mean (SD)	21 (2)
Type of surgery	
Endoscopic sinus surgery	6
Myomectomy	2
Total hysterectomy	1
Open reduction and internal fixation for Lisfranc fracture	1

ASA, American Society of Anesthesiologists

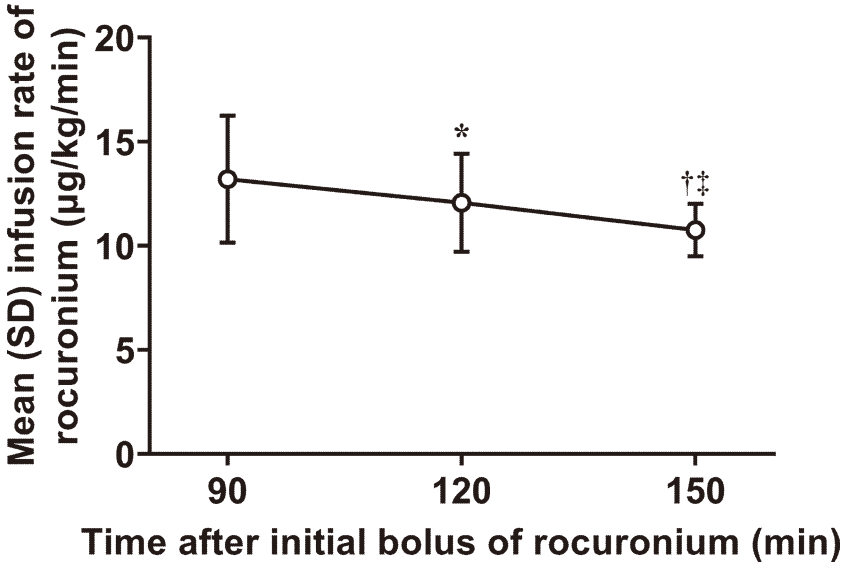

Fig. 1. Time-course of rocuronium infusion rate adjustments to maintain a deep neuromuscular block.
The infusion rate of rocuronium was adjusted to sustain neuromuscular blockade at a posttetanic count of 1 to 5 following an initial bolus of 0.6 mg/kg rocuronium. The mean (SD) infusion rates of rocuronium after the initial bolus were 13.2 (3.05) µg/kg/min at 90 minutes, 12.1 (2.35) µg/kg/min at 120 minutes, and 10.8 (1.26) µg/kg/min at 150 minutes. *$p = 0.027$ vs. infusion rate at 90 minutes after initial bolus. †$p = 0.026$ vs. infusion rate at 90 minutes after initial bolus. ‡$p = 0.041$ vs. infusion rate at 120 minutes after initial bolus.

RESULTS

A total of 10 patients were enrolled in this study (Table 1). The mean (SD) infusion rates of rocuronium after the initial bolus were 13.2 (3.05) μg/kg/min at 90 minutes, 12.1 (2.35) μg/kg/min at 120 minutes, and 10.8 (1.26) μg/kg/min at 150 minutes (Figure 1). The infusion rate of rocuronium decreased significantly over time (Figure 1). None of the patients experienced an intense neuromuscular block after continuous administration had been started. All patients achieved complete recovery from neuromuscular blockade after administration of sugammadex, with no issues.

DISCUSSION

The present study investigated the appropriate infusion rate of rocuronium and its adjustment method for maintaining a deep level of neuromuscular blockade without inducing an excessively intense block. The findings indicate that, to sustain a deep block without inducing an overly intense block, the average infusion rate 90 minutes after the first bolus was 13.2 μg/kg/min. Moreover, a gradual reduction in the infusion rate was needed to prevent an excessively intense block.

Continuous drug administration, as opposed to intermittent dosing, is considered to attenuate fluctuations in blood concentration. Maintaining a moderate neuromuscular block or 95% suppression of the single twitch height does not necessitate a reduction in the infusion rate when rocuronium is continuously infused at a rate of 5.58 (1.94) μg/kg/min[6]. However, if rocuronium continues to be infused at a high rate to maintain a deep neuromuscular block, exceeding the clearance capacity, the rocuronium concentration would be elevated. The present study demonstrates that to maintain a deep neuromuscular block while avoiding an intense block, the infusion rate must be reduced.

Deep neuromuscular block has been shown to improve surgical conditions[9–11]. In addition, rapid antagonism of the neuromuscular blockade at the end of surgery can decrease the length of stay in the operating room[12]. A combination of rocuronium and sugammadex can enable such management. Nevertheless, if sugammadex is administered at an insufficient dose, possible risks are recurarization and residual neuromuscular blocks[13–17]. The manufacturer's package insert for sugammadex does not provide a recommended dosage for an intense block or a PTC of 0, except in emergency situations, for which an excessively high dose of 16 mg/kg is indicated. Therefore, from a patient safety perspective, to administer rocuronium in a way that an intense block is not induced during surgery is considered crucial. A systematic review has revealed that the continuous infusion rate required to maintain a deep neuromuscular block at a PTC of 1 to 2 is 13.9 μg/kg/min[7]. This infusion rate was determined on the basis of the average administration rate, derived by dividing the total dose of rocuronium by the overall administration time, as reported in the referenced articles. The present study observed a close alignment with this rate at 90 minutes after the initial bolus. Regarding the adjustment of the rocuronium infusion rate, the systematic review omitted any discussion. In contrast, the present study offers compelling evidence that endorses the gradual reduction of the rocuronium infusion rate to avoid an intense block while maintaining a deep neuromuscular block. Therefore, we believe that our research findings can significantly enhance the safety of anesthesia management. Additionally, the use of quantitative neuromuscular monitoring is highly recommended when NMBAs are administered[1,3]. The present study emphasizes that the infusion rate should be adjusted on the basis of quantitative neuromuscular monitoring.

This study did not measure rocuronium concentration in blood ; therefore, comprehensive pharmacokinetic analysis could not be conducted. Additional studies are required to elucidate the mechanism.

CONCLUSIONS

The present study has determined strategies for maintaining a deep, yet not overly intense, neuromuscular blockade through continuous rocuronium infusion.

Authors have no conflict of interest.

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