Administration of rocuronium based on real body weight versus fat-free mass in patients with lymphedema

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Abstract

Objective: To compare the clinical pharmacokinetics of rocuronium when applied according to fat-free mass versus real body weight during anesthetic induction of patients with lymphedema.

Methods: Sixty patients with lymphedema (age, 18–60 years; American Society of Anesthesiologists physical status, I–II) undergoing elective surgery with general anesthesia were randomly divided into two groups. Rocuronium was administered based on the fat-free mass in 30 patients and real body weight in 30 patients. General anesthesia was induced with propofol and remifentanil by target-controlled infusion. Intubation was attempted when the onset time (T1) (time from end of bolus injection to 100% twitch depression) reached maximal inhibition, and respiratory support with mechanical ventilation was then applied. The T1, clinical duration (time from end of bolus injection to recovery of twitch tension to 25% of control), recovery index (time from 25% to 75% of recovery of T1), and dosage were recorded.

Results: Complete data were recorded for 59 patients, and there were no significant differences in the general condition, intubation condition, or median duration of action of rocuronium between the two groups. However, the median T1, recovery index, and dosage of rocuronium were significantly different.

Conclusion: Good intubation conditions and a shortened clinical duration can be obtained for patients with lymphedema when induction with rocuronium is based on the fat-free mass.

Keywords

Pharmacodynamics, rocuronium, lymphedema

Introduction

Lymphedema is a lymphatic circulation disorder with complex pathological causes.

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With the recent advancements in surgical procedures, increasing numbers of lymphedema patients now undergo surgical treatment.[1] Previous pharmacodynamics studies on rocuronium mainly focused on obese patients. The results showed that administration of rocuronium based on the fat-free mass (FFM) in obese patients achieved a neuromuscular block similar to that based on the real body weight (RBW) in patients of normal body weight, resulting in reduced interindividual variations in drug responses among obese patients.[2] Most patients with lymphedema are overweight. However, they differ from obese patients in terms of body mass composition and pathophysiological functions.[3] In the present study, we investigated the pharmacodynamics of rocuronium administered based on different body weight scalars to provide a reference for safe drug administration in patients with lymphedema.

Materials and methods

Generation information

The study was approved by the Medical Ethics Committee of Beijing Shijitan Hospital. Written informed consent was obtained from the patients before the surgical procedure. Fifty-nine patients with lymphedema who underwent elective lymphatic venous anastomosis (LVA) (upper and lower extremities) from October 2015 to May 2016 were included in the study. The patients were aged 18 to 60 years and had an American Society of Anesthesiologists physical status of I to II and body mass index (BMI) of 30 to 40 kg/m². All patients underwent nasogastric intubation before the surgery, and their Mallampati score ranged from I to III. The exclusion criteria were renal and hepatic dysfunction, allergic constitution, anticipated airway difficulties, and intraoperative blood loss of >200 ml. Patients were randomly divided into two groups: Group A (based on FFM) and Group B (based on RBW).

General anesthesia

Before anesthesia, all patients were routinely monitored via electrocardiography, peripheral oxygen saturation, heart rate, and blood pressure using multi-parameter anesthesia monitors. The bispectral index (BIS) was recorded with a BIS monitor. Ringer's sodium acetate was administered via peripheral intravenous infusion.

Anesthesia was induced with propofol (plasma concentration of 3–4 µg/ml) and remifentanil (effect site concentration of 3–6 ng/ml) by target-controlled infusion (TCI). When the BIS reached 60, all patients in each group was given a bolus intravenous injection of rocuronium (0.6 mg/kg, twice the effective dose in 95% of the population [ED95] of rocuronium).[4]

Drug administration in Group A was based on the FFM:

$$FFM_{Male} = 9.27 \times 10^3 \times \text{total body weight}/(6.68 \times 10^3 + 216 \times BMI)$$
$$FFM_{Female} = 9.27 \times 10^3 \times \text{total body weight}/(8.78 \times 10^3 + 244 \times BMI)$$
$$BMI = \text{body weight (kg)/height (cm)}^{2}\ [5]$$

Drug administration in Group B was based on the RBW.

Calibration of neuromuscular blockade was initiated before rocuronium injection. Acceleromyography (TOF-Watch SX Organon Limited, Co. Dublin Ireland Monitor) was used to evaluate the degree of neuromuscular blockade at the adductor pollicis muscle using train-of-four stimulations. Tracheal intubation was attempted when the first twitch of train-of-four (onset time, T1) reached maximal depression, and mechanical ventilation was used to maintain the end-tidal carbon dioxide pressure at 35 to 45 mmHg. When T1 recovered to 25% of the baseline value, patients in Group A were administered a supplementary dose of rocuronium (0.3 mg/kg, ED95) based on the FFM, and those in Group B were administered 0.3 mg/kg of rocuronium based on the RBW. General anesthesia was maintained with

propofol and remifentanil by TCI, and the BIS was maintained at 45 to 55. TCI was discontinued 20 min before the end of surgery. After regaining spontaneous respiration and consciousness, the patients were extubated and sent to the recovery room.

Indicators for evaluation

The rocuronium dosage, T1 (time from end of bolus injection to 100% twitch depression), maximum depression of T1, clinical duration (time from end of bolus injection to recovery of twitch tension to 25% of baseline), and recovery index (time lapse of recovery from 25% to 75% of T1) were recorded, and the coefficient of variation of each parameter was calculated. Intubation conditions were assessed using the Cooper scoring system: a total score of 8 to 9 was considered excellent, 6 to 7 good, 3 to 5 fair, and 0 to 2 poor.[6]

Statistical analysis

The aim of this study was to compare the effects of rocuronium between two types of administration in patients with lymphedema undergoing surgery. With statistical significance set at 0.05, power at 80%, and loss-to-follow-up at about 6%, the estimated sample size of each group was 68. In total, 140 patients were finally enrolled in this study.

A biostatistician who did not participate in the data management or analysis used SAS 9.2 software (SAS Institute, Cary, NC) to generate random numbers in a 1:1 ratio. The results of randomization were sealed in sequentially numbered envelopes. Patients with lymphedema were then consecutively recruited and randomly assigned to one of the two above-described groups. The biostatistician, patients, and doctors were blinded to the treatment allocation.

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL). The total dosage, T1, clinical duration, and recovery index are presented as mean ± standard deviation. The differences in these indicators between the two groups were analyzed with an independent-samples t test. Other indexes, including sex and type of surgery, were compared with the χ^2 test. A P value of < 0.05 was considered statistically significant.

Results

Comparison of general conditions between Groups A and B

All patients had complete statistical data. There were no significant differences between the two groups of patients in terms of sex, age, BMI, FFM, or type of surgery. Therefore, the two sets of data were comparable (Table 1).

Table 1. Comparison of general conditions between the two groups.

Group	Patients (n)	Sex Male (n)	Sex Female (n)	Age (years)	BMI (kg/m²)	FFM (kg)	Type of surgery (n) Upper extremity anastomosis	Type of surgery (n) Lower extremity anastomosis
A	30	9	21	41 ± 6	36 ± 2	52 ± 1	22	8
B	29	7	22	43 ± 5	35 ± 1	49 ± 2	21	8
P				>0.05	>0.05	>0.05		

Data are presented as mean ± standard deviation.
BMI: body mass index, FFM: fat-free mass.

Table 2. Comparisons of rocuronium onset time, rocuronium dosage, and Cooper scores between the two groups.

Group	Patients (n)	Onset time (s)	Clinical duration (min)	Recovery index (min)	Dosage (mg/h)	Cooper score
A	30	75.1 ± 6.9	44.8 ± 3.9	2.2 ± 0.5	41.5 ± 4.5	8.6 ± 0.7
B	29	58.1 ± 5.2	51.6 ± 5.9	5.3 ± 0.8	58.2 ± 5.6	8.3 ± 0.9
P		<0.05	>0.05	<0.05	<0.05	>0.05

Data are presented as mean ± standard deviation.

Patients in Group B had a longer clinical duration of rocuronium than those in Group A; however, this difference was not statistically significant. Statistically significant differences were observed in the T1, recovery index, and dosage between the two groups ($P < 0.05$). No significant difference was observed between the two groups in the intubation condition as assessed by the Cooper score or in the first-pass intubation success rate (Table 2).

Discussion

Lymphedema can be classified as primary or secondary. Primary lymphedema is hereditary, whereas secondary lymphedema is mainly caused by surgical treatment of tumors, radiotherapy and chemotherapy, lymphatic obstruction, and chronic venous insufficiency.[7] For this select group of patients, the lack of neuromuscular monitoring will lead to difficulties for anesthesiologists in terms of deciding whether to administer a supplementary dose of the neuromuscular blocking agent and determining the timing of administration. When the supplementary dose is administered based solely on past experience, it often results in prolonged action of the neuromuscular blocking agents, leading to side effects such as postoperative residual neuromuscular blockade.

Clinically, dosage calculation for neuromuscular blocking agents is based on the RBW and ED95. However, there is substantial interindividual variation in the response to neuromuscular blocking agents among patients with special body mass compositions. Therefore, evidence-based medicine has been increasingly proving the rationality of drug administration based on the corrected body weight in this special population. Although patients with lymphedema are not equivalent to obese patients, most are overweight, which will also affect the volume of distribution, plasma concentration, and elimination half-life of neuromuscular blocking agents.

Previous studies on the clinical application of neuromuscular blocking agents in obese patients have shown that changes in the pathophysiological functions and body mass composition of obese patients could affect the pharmacodynamics of these drugs. Meyhoff et al.[2] showed that calculation of the rocuronium dosage should be based on the ideal body weight of obese patients to avoid a prolonged onset time of neuromuscular blocking agents. Wang et al.[8] found that while administration of rocuronium based on the body surface area did not reduce interindividual variations in the onset of neuromuscular blockade, the total drug dosage required was reduced. In contrast, Meyhoff et al.[2] reported that administration of rocuronium based on the FFM achieved a clinical duration in obese patients similar to that in patients of normal body weight, while also reducing interindividual variation in pharmacodynamics among obese patients.

The target sites of neuromuscular blocking agents are located at the neuromuscular junctions, and the lean body mass determines the number of neuromuscular junctions.[8] Furthermore, the pharmacological effect of a neuromuscular blocking agent is primarily dependent on its plasma concentration, which is closely associated with the blood volume. Nondepolarizing neuromuscular blocking agents are mainly distributed in the lean muscles because of their high water solubility and low fat solubility. Therefore, calculation of the administration dosage of these agents is more accurate and reasonable when based on the FFM than on the RBW.[2] Our study also showed that for patients with lymphedema, the FFM is a better body weight scalar than the RBW for the administration of rocuronium. The widely accepted Janmahasatian formula was applied to calculate the lean body weight in the present study. This formula allows for a more accurate calculation of the lean body weight of patients with lymphedema.[5]

Substantial variations in lymphatic drainage occur before and after LVA and may affect the plasma protein volume and concentration. This is especially true for drugs with high fat solubility and may result in fluctuations in the drug plasma concentration. Research related to the lymphatic circulatory system is less advanced than that related to the blood circulatory system. We hope that further investigations will be conducted on the changes in the circulation steady state during LVA and lymphatic liposuction and their effects on drug concentrations and pharmacodynamics.

Conclusion

Good intubation conditions and a shortened clinical duration can be obtained for patients with lymphedema when induction with rocuronium is based on the FFM.

Authors' contributions

Zhang Jing: patient selection and recruitment, statistical analysis, and writing of the manuscript. Aikeremujiang Muheremu: writing of the manuscript. Liu Pengfei, Hu Xiaoyun: modification of the manuscript and data collection. Zhao Binjiang: study design and anesthetic procedure.

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