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ORIGINAL ARTICLE

A randomized trial to identify optimal precurarizing dose of rocuronium to avoid precurarization-induced neuromuscular block

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Abstract
Purpose The aim of this study was to examine the safe precurarizing dose of rocuronium required to avoid neuromuscular block after precurarization.
Methods Twenty-four female patients were randomly allocated into two groups of 12 patients each. General anesthesia was induced and maintained with remifentanil and propofol, and a laryngeal mask was inserted without the aid of a neuromuscular blocking agent. Patients were randomized to receive either 0.03 or 0.06 mg/kg rocuronium as a precurarizing dose. Neuromuscular block was monitored using acceleromyographic train-of-four (TOF) of the adductor pollicis muscle. Three minutes after the precurarization, all patients received suxamethonium 1.5 mg/kg and were graded on severity of fasciculations.
Results The average TOF ratio was kept above 0.9 even 3 min after precurarization with 0.03 mg/kg rocuronium. In contrast, in patients who received 0.06 mg/kg rocuronium, the ratios significantly decreased to 0.72 (0.14) [mean (SD), $P < 0.004$] and 0.68 (0.18) ($P < 0.006$) 2 min and 3 min after the precurarization, respectively. No visible muscle movement was observed following suxamethonium injection, except that one patient who received 0.03 mg/kg rocuronium showed very fine muscle movements of the fingertips.
Conclusion Rocuronium at 0.06 mg/kg is an overdose for precurarization. The results of the present study demonstrate that a safe and effective precurarizing dose of rocuronium is 0.03 mg/kg.

Keywords Precurarization · Rocuronium · Suxamethonium · Neuromuscular block

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Introduction

Many anesthetics can reduce lower and upper esophageal sphincter tone and tend to promote gastroesophageal regurgitation into the pharynx [1]. Therefore, rapid sequence intubation is frequently used to decrease the risk of pulmonary aspiration of gastric contents in a patient with a full stomach. Suxamethonium enables us to considerably shorten the interval from the patient's loss of consciousness following hypnotics to tracheal intubation and is considered to be appropriate for rapid sequence intubation [2, 3]. For such occasions, precurarization with a small dose of a nondepolarizing neuromuscular blocking agent has been widely used to prevent muscle fasciculation induced by suxamethonium and rise in intraabdominal pressure [3–6]. However, the technique may cause difficulty in breathing [7, 8], gastroesophageal regurgitation, and pulmonary aspiration associated with overdosage of precurarization [9]. The theoretical calculation using published pharmacodynamic and pharmacokinetic data showed that a dose of rocuronium equivalent to 10% of the ED_{95} (ED_{95} = 0.3 mg/kg) would rarely produce a measurable neuromuscular effect and should be therefore recommended as an appropriate dose for precurarization [10]. However, in previous studies [5, 11–13], 20–30% of the ED_{95} of rocuronium was generally used for precurarization, and effectiveness for defasciculation was examined. Although it is anticipated that a larger dose of rocuronium can greatly

suppress suxamethonium-induced fasciculation, the risk of a significant neuromuscular block in several minutes after the precurarization dosing may become greater. Unfortunately, the neuromuscular effect of precurarization has never been certified with any objective neuromuscular monitoring in clinical settings. Therefore, the main purpose of this study was to identify the optimal dose of rocuronium to avoid both neuromuscular block associated with precurarization and fasciculation induced by suxamethonium.

Materials and methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 24 adult female patients consented to participate in this study. Patients were ASA physical status I or II, 20–60 years of age, undergoing elective surgery. None of the patients had a difficult airway, previous history of hypertension, neuromuscular, hepatic, and renal disorders, or was taking any drug known to interact with neuromuscular blocking agents. Patients whose body mass index (BMI) was $\geq$25 or <18.5 were also excluded from the study. Premedication consisted of orally administered ranitidine 150 mg the night before and on the morning of surgery and i.m. midazolam 0.03–0.04 mg/kg. On arrival at the operating room, all patients were monitored with ECG, noninvasive blood pressure measurement, and pulse oximetry. An i.v. infusion of acetated Ringer's solution, 8–10 ml/kg/h, was started via the intravenous route. Anesthesia was induced with a continuous infusion of remifentanil at 0.5 μg/kg/min and a bolus of propofol 2 mg/kg. After confirming the bispectral index value of 60 or less (BIS monitor A-2000; Aspect Medical Systems, Norwood, MA, USA), a laryngeal mask was inserted without the aid of a neuromuscular blocking agent. Anesthesia was maintained with remifentanil 0.2 μg/kg/min and propofol 4–6 mg/kg/h. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a Multigas Unit AG-920R (Nihon Kohden, Tokyo, Japan). Patient rectal temperature was monitored using a Mon-a-Therm (Mallinckrodt; Anesthesia Products, St. Louis, MO, USA) and was maintained at >36°C using a warming mattress and blanket (Thermacare and Medi-Therm II; Gaymer Industries, NY, USA) and warmed i.v. fluids. Skin temperature over the thenar muscle was recorded every 15 s throughout the experiment using a surface probe equipped in an acceleromyographic device and maintained at >32°C. After a stable depth of anesthesia was obtained, the unilateral ulnar nerve was stimulated at the wrist with supramaximal and square-wave stimuli of 0.2-ms duration, which was delivered in a train-of-four (TOF) mode at 2 Hz every 15 s. Contraction of the ipsilateral adductor pollicis was measured using an acceleromyograph (TOF-Watch SX; Organon, Dublin, Ireland). After the control TOF stimuli were administered for a minimum of 10 min to stabilize the responses [14], the T_1 value was readjusted to 100% and the patients received a precurarizing dose of rocuronium at either 0.03 or 0.06 mg/kg via computer-generated randomization. During a waiting time of 3 min, the time course of the TOF ratios was recorded. The TOF ratios were normalized by the baseline values [14]. Three minutes after the precurarizing dose, all patients received suxamethonium 1.5 mg/kg i.v. and were graded on severity of fasciculation using a four-point scale (0, no visible muscle movement; 1, very fine muscle movement of the face or the fingertips; 2, small fasciculations on the trunk and/or extremities; 3, strong fasciculations on the trunk and/or extremities) [12] by a staff anesthesiologist who was blinded to the grouping. Onset from the time of administration of suxamethonium to maximum depression of T_1 was monitored.

The results of the previous study showed that the fourth twitch height was significantly larger than the T_1 height when the TOF responses were measured by acceleromyography and before an injection of neuromuscular blocking agent. Calculation of sample size was based on the averaged baseline TOF ratio was 1.11 (0.09) [mean (SD)] [14], and a significant neuromuscular block induced by precurarization was defined as less than 90% [15] of the baseline TOF ratio ($1.11 \times 0.9 = 0.99$). For the results to have statistical significance with $\alpha = 0.05$ and $\beta = 0.80$, one needed to recruit 10 patients in each group. To allow for dropouts, we enrolled 12 patients in each group. Data are presented as mean (SD). Statistical analysis was performed using StatView software for Windows (SAS Institute, Cary, NC, USA). Analysis of variance was used for multiple comparisons. If a significant P value of <0.05 was obtained in multiple comparisons, further group comparisons were made using the Bonferroni post hoc test. Unpaired Student's t test was used for two-group comparisons. A P value <0.05 was considered statistically significant.

Results

Data from all 24 patients could be included in the analyses. Patient characteristics did not differ between the two groups (Table 1). In 0.03 mg/kg group, an averaged TOF ratio was maintained above 0.9 even 3 min after precurarization (Table 2), and a significant depression in the TOF ratio was shown only in 3 patients, at 2 and 3 min after precurarization, but the ratio was maintained at more than 0.7 (Fig. 1a). In the 0.06 mg/kg group, a significant neuromuscular block was observed in all patients (Fig. 1b),

and averaged TOF ratios significantly decreased to 0.72 (0.13) ($P < 0.004$) and 0.66 (0.16) ($P < 0.006$), at 2 and 3 min, respectively, after precurarization (Table 2). No visible muscle movement (scale 0) was observed following suxamethonium injection, except in 1 patient who had received 0.03 mg/kg rocuronium and showed very fine muscle movements of the fingertips (scale 1). There was a statistically significant difference in the onset times of suxamethonium-induced neuromuscular block between the 0.03 mg/kg group [79.5 (12.3) s, $P = 0.032$] and the 0.06 mg/kg group [93.9 (14.5) s].

Discussion

The present study could identify that a safe precurarizing dose of rocuronium for surgical patients was 0.03 mg/kg. The dose of about 0.06 mg/kg rocuronium that had been commonly studied for precurarization [5, 11, 12] induced a potentially risky neuromuscular block within 3 min while awaiting induction of anesthesia and was therefore regarded as overdosing. Furthermore, to effectively prevent suxamethonium-induced muscle fasciculation, rocuronium 0.03 mg/kg was proven to be a sufficient dose.

Suxamethonium has the superior feature of rapid onset of action and enables shortening the interval from the patient's loss of consciousness following hypnotics to tracheal intubation. Particularly in an emergent patient with a full stomach, the incidence of pulmonary aspiration during induction of general anesthesia will be three to four times higher than that for patients undergoing proposed elective surgery [16]. Therefore, establishing a fast and profound neuromuscular block is required for rapid sequence intubation. Although priming [17] and timing principles [18] using rapid-onset rocuronium have been reported to be effective for rapid sequence intubation, suxamethonium seems to be clinically preferred rather than rocuronium as a neuromuscular blocking agent for patients with specific risks of pulmonary aspiration. In fact, a survey of variation of rapid sequence induction techniques in Wales reported that suxamethonium was currently used for 97% of cesarean sections, 94% of bowel obstructions, and 85% of appendectomies; in contrast, rocuronium was used only in 2–12% of patients [2]. A retrospective case-review analysis of 250 patients undergoing appendectomy in a 1-year period also revealed that suxamethonium use was 80%, with 96% of these patients receiving rocuronium precurarization [3]. To prevent several side effects associated with suxamethonium-induced muscular fasciculation, including an increase in intragastric pressure, precurarization seems to be important. The barrier pressure, which is the difference between intragastric pressure (mean value, 10 cmH_2O) and lower esophageal sphincter pressure (36 cmH_2O) normally prevents reflux of gastric contents into the esophagus [19]. However, in patients with a full stomach, basal intragastric pressure may rise, and many induction anesthetics reduce the lower esophageal sphincter tone [1]. In addition, it should not be surprising that intragastric pressure rises as high as 40 cmH_2O as a result of suxamethonium-induced fasciculation [20]. Under specific conditions in which the lower sphincter is not closing tightly enough, precurarization may be necessary to prevent fasciculation because the increases in intragastric pressure are directly related to the intensity of fasciculation [20]. As just described, such a combination of precurarization with rocuronium and suxamethonium is still predominantly used for rapid sequence induction and therefore should be safely and effectively applied. The present study is considered meaningful to be able to optimize the precurarizing dose of rocuronium in clinical anesthesia. Based on the results of this study, rocuronium 0.03 mg/kg is sufficient to prevent fasciculation on the trunk and may avoid increasing intraabdominal pressure.

Table 1 Patient characteristics

	0.03 mg/kg group	0.06 mg/kg group
Age (years)	40.2 (12.0)	37.6 (11.5)
Weight (kg)	54.3 (5.4)	56.2 (8.0)
Height (cm)	158.5 (4.9)	161.2 (8.0)

Data are presented as mean (SD); no significant differences were seen between the groups

Table 2 Change in the train-of-four (TOF) ratios after precurarization

	1 min	2 min	3 min
0.03 mg/kg group	1.01 (0.01)	0.94 (0.09)	0.91 (0.12)
	(range, 0.98–1.03)	(range, 0.79–1.05)	(range, 0.70–1.06)
0.06 mg/kg group	0.98 (0.04)	0.72 (0.13)*	0.66 (0.16)*
	(range, 0.89–1.04)	(range, 0.54–0.97)	(range, 0.37–0.88)

Data are presented as percent (%) of control and mean (SD) (range)

* $P < 0.05$ when compared with the baseline value

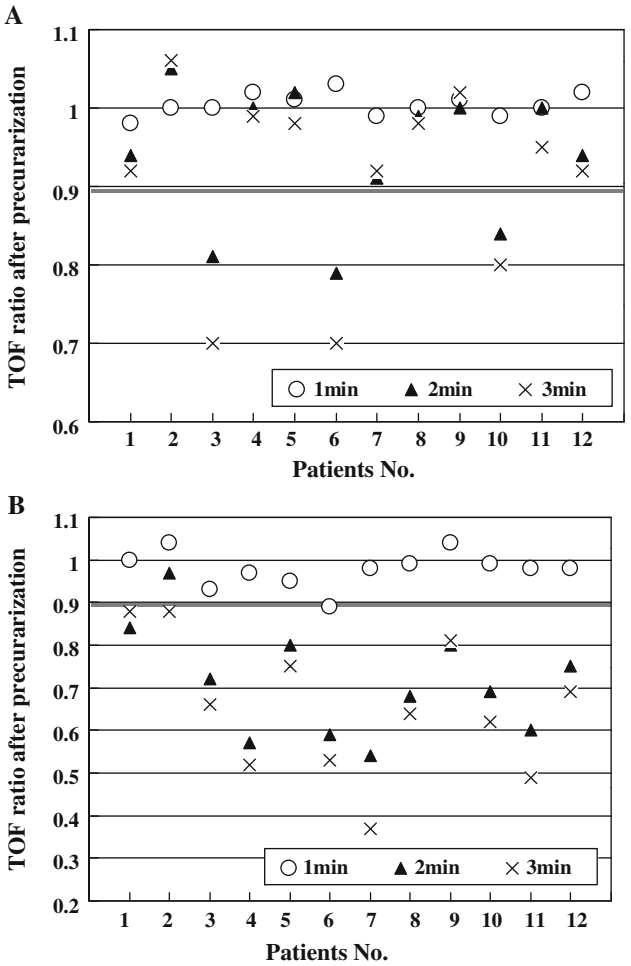

Fig. 1 Detailed train-of-four (*TOF*) ratios after precurarization in each patient in 0.03 mg/kg group (**a**) and 0.06 mg/kg group (**b**). Data were normalized by each baseline train-of-four ratio recorded before precurarization. *Circles*, *triangles*, and *multisymbols* on the graph show the train-of-four ratios observed 1, 2, and 3 min after precurarization, respectively

It was reported that rocuronium was the best drug to prevent muscle fasciculation following suxamethonium injection [5]. In the study, a pretreatment of 0.06 mg/kg rocuronium and an interval of 4 min to suxamethonium injection could completely prevent fasciculation in 85% of patients. Suxamethonium-induced fasciculation certainly would be effectively inhibited if the pretreatment dose of rocuronium was greater than a nonparalyzing dose. However, the intensity of neuromuscular block induced by the precurarizing dose of rocuronium was not clarified even though neuromuscular function was monitored throughout the study [5]. Three minutes after the precurarizing dose of 0.06 mg/kg rocuronium, we could show that an averaged TOF ratio was significantly depressed from 1.0 to 0.68. A TOF ratio below 0.9 observed at the adductor pollicis muscle exposes awake patients to the potentially unpleasant experience of difficulty in swallowing. At that time, the upper esophageal sphincter muscle resting tone markedly decreases [15]. Although precurarization should be applied to patients with a full stomach, it seems very possible that the risk of pulmonary aspiration of gastric contents may be even higher when rocuronium is overdosed [9]. It is therefore suggested, from our results, that the appropriate dose of rocuronium for safe and effective precurarization is 0.03 mg/kg.

Precurarization with a nondepolarizing neuromuscular blocking agent can prevent fasciculation; however, this simultaneously reduces the neuromuscular blocking potency of suxamethonium and also delays the onset of depolarizing neuromuscular block [21]. In the present study, a faster onset of suxamethonium-induced neuromuscular block was obtained in patients pretreated with 0.03 mg/kg rocuronium. It should be considered that too large a precurarization dose may conversely make suxamethonium less effective and delay the timing of tracheal intubation.

We set the administration interval between the precurarizing dose of rocuronium and suxamethonium to 3 min in accordance with conventional practice. Timing of administration is important, because the benefits of precurarization may be weakened if suxamethonium is given too soon or, equally, if it is given too late. Based on the characteristics of rapid onset and intermediate duration of action of rocuronium, a longer waiting time for suxamethonium accelerates rocuronium to dissociate from the neuromuscular junction. Further studies are warranted to clarify a relationship between the precurarizing dose of rocuronium and the waiting time to suxamethonium administration.

In this study, the neuromuscular effects of precurarizing doses of rocuronium were observed during maintenance of anesthesia. Twitch responses evoked by the repetitive TOF mode gradually increase during baseline stimulation and reach a plateau at around 10 min [14]. In the middle of the staircase phenomenon, neuromuscular block induced by a small dose of rocuronium might not be correctly evaluated; therefore, the present study required stabilizing the responses before precurarization. In the protocol of this study, not only the effects of precurarization but also other influencing factors on the degree of neuromuscular block must be considered. The duration of anesthesia with opioid and propofol before an administration of neuromuscular blocking agent increases the intensity of neuromuscular block [22]. In addition, the longer duration of baseline nerve stimulation can further decrease the onset of action of rocuronium [23]. It is likely that the peripheral vasodilation caused by anesthetics and muscle blood flow increased by muscle contractions to nerve stimulation may be involved in the augmentation of neuromuscular block. It is possible that an optimal precurarizing dose of

rocuronium may be larger in awake patients who are not peripherally stimulated by a nerve stimulator.

The patients enrolled in this study were all Japanese women. Asian people are more sensitive to rocuronium-induced block than Caucasian people [24]. Racial differences may therefore impact on the optimal dose of rocuronium for precurarization. In addition, women are more sensitive to rocuronium and require about 30% less rocuronium than men to achieve the same degree of neuromuscular block [25]. However, it was reported that a precurarizing dose of rocuronium affected men and women equally [26].

In conclusion, precurarization with 0.03 mg/kg rocuronium induces no significant depression of the TOF ratios in most patients during a waiting time of 3 min and can certainly prevent suxamethonium-induced fasciculation. We consider that 0.06 mg/kg rocuronium causes a marked neuromuscular block that potentially triggers pulmonary aspiration of gastric contents.

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Conflict of interest No relationships between authors and any company or organization with a vested interest in the outcome of the study.

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