Optimal precurarizing dose of rocuronium to decrease fasciculation and myalgia following succinylcholine administration

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Background: Succinylcholine commonly produces frequent adverse effects, including muscle fasciculation and myalgia. The current study identified the optimal dose of rocuronium to prevent succinylcholine-induced fasciculation and myalgia and evaluated the influence of rocuronium on the speed of onset produced by succinylcholine.

Methods: This randomized, double-blinded study was conducted in 100 patients randomly allocated into five groups of 20 patients each. Patients were randomized to receive 0.02, 0.03, 0.04, 0.05 and 0.06 mg/kg rocuronium as a precurarizing dose. Neuromuscular monitoring after each precurarizing dose was recorded from the adductor pollicis muscle using acceleromyography with train-of-four stimulation of the ulnar nerve. All patients received succinylcholine 1.5 mg/kg at 2 minutes after the precurarization, and were assessed the incidence and severity of fasciculations, while myalgia was assessed at 24 hours after surgery.

Results: The incidence and severity of visible muscle fasciculation was significantly less with increasing the amount of precurarizing dose of rocuronium (P < 0.001). Those of myalgia tend to decrease according to increasing the amount of precurarizing dose of rocuronium, but there was no significance (P = 0.072). The onset time of succinylcholine was significantly longer with increasing the amount of precurarizing dose of rocuronium (P < 0.001).

Conclusions: Precurarization with 0.04 mg/kg rocuronium was the optimal dose considering the reduction in the incidence and severity of fasciculation and myalgia with acceptable onset time, and the safe and effective precurarization.

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Key Words: Fasciculation, Myalgia, Neuromuscular blockade, Precurarization, Rocuronium, Succinylcholine.
Introduction

Succinylcholine has been still used in anesthesia to produce profound neuromuscular blockade of rapid onset and short duration [1]. Succinylcholine commonly produces frequent adverse effects, including muscle fasciculation and myalgia. Although these effects are minor, myalgia, which can be accompanied by muscle stiffness, can induce significant discomfort in some patients [2]. Pretreatment with d-tubocurarine, vecuronium, rocuronium, mivacurium, gallamine, magnesium and atracurium has been considered to prevent muscle fasciculation and myalgia induced by succinylcholine [3]. Pretreatment with small doses (10% of the 95% reduction in twitch tension [ED95]) of rocuronium before succinylcholine administration would rarely produce a measurable neuromuscular effect, and therefore would be recommended as an appropriate precurarizing dose in the computer simulation [4]. However, 0.06–0.1 mg/kg of rocuronium (20–30% of the ED95) has been recommended as a precurarizing dose of succinylcholine 1.5 mg/kg clinically [5,6]. Although a larger dose of rocuronium (20% of the ED95) can greatly suppress succinylcholine-induced fasciculation, the risk of a significant neuromuscular block in three minutes following the precurarization may be increased [7]. Fukano et al. [8] reported that 0.03 mg/kg rocuronium was recommended for safe and effective precurarizing dose in 3 min before succinylcholine. However, the effect of this dose to prevent fasciculations and postoperative myalgia from succinylcholine was not evaluated.

The aim of the present study was to identify the optimal dose of rocuronium to prevent succinylcholine-induced fasciculation and myalgia and to evaluate the influence of rocuronium on the speed of onset produced by succinylcholine.

Materials and Methods

The Hospital Ethics Committee approved this study protocol and written informed consent was obtained from all patients after the aim and potential risks of the study were fully explained to each. One hundred patients, aged 20 to 58 years, with an American Society of Anesthesiologists physical status of I or II undergoing elective surgery with a general anesthesia in the supine position were studied in a double blind randomized study. Patients were excluded for the following reasons: neuromuscular, cardiovascular, hepatic, or renal diseases, an age < 18 or > 65 years, those with body weight 20% greater than ideal body weight, with a history of drug abuse, and with an anticipated difficult intubation. Patients were divided into five groups. Twenty patients were allocated randomly to each pretreatment group: 0.02 mg/kg rocuronium (Group 0.02), 0.03 mg/kg rocuronium (Group 0.03), 0.04 mg/kg rocuronium (Group 0.04), 0.05 mg/kg rocuronium (Group 0.05) and 0.06 mg/kg rocuronium (Group 0.06) (Fig. 1).

No premedication was given. Monitoring, established on ar-

![Fig. 1. Flow chart of the study.](image-url)
rival in the operating room, included electrocardiography, non-
invasive arterial pressure, oxygen saturation, capnography and a
bispectral index (BIS) monitor (Model A 2000, Aspect Medical
Systems, Natick, MA, USA). Neuromuscular function was as-
essed using acceleromyography of the adductor pollicis muscle
(TOF-Watch SX®, Organon Ltd., Dublin, Ireland). Before plac-
ing the surface electrodes, the skin overlying the ulnar nerve was
cleansed with isopropyl alcohol. Two electrodes (Cleartrode™,
Ref 1720-003, ConMed®, Utica, NY, USA) were placed over the
prepared skin. A force transducer was fixed to the thumb.

General anesthesia was induced with remifentanil 0.5 μg/kg/min
injected intravenously over 2 minutes (min) followed by propo-
fol 2–2.5 mg/kg injected intravenously over 30 seconds (s). As
soon as a patient lost consciousness, ventilation via facemask
with a fresh gas flow at 4 L/min (50% air in oxygen) controlled
manually to maintain the end-tidal CO₂ at 30 to 35 mmHg and
neuromuscular monitoring began immediately. The fingers were
tightly fixed to the armboard after a 5-s 50-Hz tetanic stimulus
over ulnar nerve. The calibration and supramaximal stimulation
were achieved by the built-in calibration function (CAL 2) of the
acceleromyography. Train-of-four (TOF) stimulation (0.2 ms
duration at 2 Hz with supramaximal current) was repeated every
15 s. After stabilization of control responses (< 5% variation in
the first twitch and TOF), each precurarizing dose of rocuroni-
um was administered via computer-generated randomization.
The time course of the TOF ratios was collected on a computer
monitored throughout the endotracheal intubation. At 2 min
after the pretreatment of rocuronium, all patients received suc-
cinylcholine 1.5 mg/kg. Fasciculations were evaluated by an
investigator blinded to the patient’s group assignment and were
graded according to a four-point rating scale: 0 = no fascicula-
tion, 1 = mild, fine fasciculation of the eyes, neck, face or fingers
without limb movement, 2 = moderate fasciculation involving
limbs and/or trunk, 3 = severe fasciculation with movement of
one or more limbs and/or movements requiring forceful reten-
tion [9]. Onset from the time of administration of succinylcho-
iline to maximum depression of first twitch of TOF stimulation
was recorded. Tracheal intubation was performed at the max-
imum depression of first twitch. Anesthesia was maintained with
1–1.5 minimum alveolar concentration of sevoflurane in order
to hold the BIS lower than 50 after endotracheal intubation. An-
algesia was provided by 0.05–0.2 μg/kg/min remifentanil during
the surgery. The incidence and severity of postoperative myalgia
and the consumption of fentanyl in patient controlled analge-
sia (PCA) was assessed at 24 hours postoperatively by another
investigator who was unaware of injection details, using a four-
point rating scale and graded as 0 = no muscle pain, 1 = muscle
stiffness limited to one area of the body, 2 = muscle pain or stiff-
ness noticed spontaneously complained of by the patient that
requires analgesics, 3 = incapacitating generalized, severe muscle
stiffness or pain [10].

Statistical analyses were performed using SPSS statistical soft-
ware, version 17.0 (SPSS Inc, Chicago, IL, USA). In this study,
the sample size calculation was taken from the previous results
[8]. On the basis of a relevant 20% change (SD 17% change) in
the onset time (79.5 ± 12.3 s) of succinylcholine with pretreat-
ment of rocuronium 0.03 mg/kg, we calculated that 17 patients
in each 5 groups could test the null hypothesis at 0.05 signifi-
cance with a power of 0.80. We enrolled 20 patients to account
for a 10% drop out rate. Analysis of variance (ANOVA) was
performed for continuous variables (i.e., age, weight, height, on-
set time, and fentanyl consumption) and multiple comparisons
were made with the Bonferroni post hoc test when the results
were significant. Repeated-measure ANOVA was used to com-
pare the TOF ratios between 1 and 2 min after precurarizing
dose. The Kruskal-Wallis ANOVA with Tukey test for post hoc
analysis was used to determine the significance of differences
with respect to incidence and severity of the fasciculation and
myalgia. The data were expressed as the mean ± SD (number,%).
Differences were considered statistically significant if P < 0.05.

Results

Among the 100 patients recruited in this study none was
excluded. There were no differences in patient characteristics
between groups (Table 1). An averaged TOF ratio at 2 min was
significantly decreased from 98 ± 4% (Group 0.02) to 76 ± 10%
(Group 0.06) with increasing the amount of precurarizing dose
of rocuronium (P < 0.001) (Table 2). Less than 80% of TOF ratio
was occurred in more than 40% of subjects after precurarizing

| Table 1. Demographic Data |
|---------------------------|
| Group 0.02 | Group 0.03 | Group 0.04 | Group 0.05 | Group 0.06 | P    |
| --- | --- | --- | --- | --- | --- |
| n     | 20 | 20 | 20 | 20 | 20 |
| Age (yr) | 41.7 ± 10.4 (21–58) | 37.8 ± 8.9 (24–47) | 37.8 ± 11.6 (20–55) | 43.2 ± 9.2 (22–58) | 36.1 ± 9.6 (20–50) | 0.135 |
| M/F   | 8/12 | 9/11 | 7/13 | 8/12 | 9/11 | 0.966 |
| Weight (kg) | 60.2 ± 10.6 | 62.4 ± 12.7 | 60.1 ± 10.6 | 60.3 ± 10.4 | 65.0 ± 10.5 | 0.573 |
| Height (cm) | 163.2 ± 10.1 | 164.9 ± 8.5 | 163.7 ± 8.4 | 166.8 ± 9.7 | 163.7 ± 9.1 | 0.725 |

Values are presented as mean ± SD (range) or numbers of patients. Group 0.02: rocuronium 0.02 mg/kg. Group 0.03: rocuronium 0.03 mg/kg. Group 0.04: rocuronium 0.04 mg/kg. Group 0.05: rocuronium 0.05 mg/kg. Group 0.06: rocuronium 0.06 mg/kg. P using analysis of variance.
The principal findings of this study were the incidence and severity of visible muscle fasciculation was significantly less with increasing the amount of precurarizing dose of rocuronium (P < 0.001). Those of myalgia tend to decrease according to increasing the amount of precurarizing dose of rocuronium, but there was no significant (P = 0.072). The onset time of succinylcholine was significantly longer with increasing the amount of precurarizing dose of rocuronium (P < 0.001). The precurarizing dose of rocuronium 0.04 mg/kg showed lower incidence of fasciculation than Group 0.02 and Group 0.03, and maintaining the clinically acceptable onset time than Group 0.05 and Group 0.06 (Fig. 2).

Succinylcholine-induced fasciculation and postoperative myalgia are a well-recognized side effect with the reported incidence of 95% and 50%, respectively [3]. Myalgia after the use of succinylcholine administration [3]. However, the risk of potentially serious adverse events (blurred vision, diplopia, heavy eyelids, muscle weakness, difficulty in swallowing, and voice disorder) with muscle relaxants is not negligible [5]. In the previous study, a pretreatment of 0.06 mg/kg rocuronium before succinylcholine injection occurred the depression of an averaged TOF ratio from 100 to 68% [8]. In this study, we also found an averaged TOF ratio was depressed to 84 ± 10% and 76 ± 10% after rocuronium.

**Table 2.** Change in the Train-of-four (TOF) Ratios (%) after Each Precurarizing Dose of Rocuronium and Onset Time of Succinylcholine

| Precurarizing dose (μg) | Group 0.02 | Group 0.03 | Group 0.04 | Group 0.05 | Group 0.06 | P |
|------------------------|------------|------------|------------|------------|------------|---|
| Number (%) with fasciculation | 1 min | 2 min | 18 (90%) | 15 (75%) | 6 (30%) | 5 (25%) | 4 (20%) | 0.072 |
| Fasciculation scores | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 | 0.072 |
| Number (%) with myalgia | 2 (10%) | 3 (20%) | 4 (20%) | 5 (25%) | 6 (30%) | 15 (75%) | 18 (90%) | 14 (70%) | 0.072 |
| Myalgia scores | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 | 0.072 |
| Fentanyl (μg) | 752.8 ± 143.6 | 834.5 ± 166.5 | 802.7 ± 157.8 | 754.5 ± 139.8 | 786.3 ± 147.9 | 0.396 |

Values are presented as mean ± SD, or numbers (%). Group 0.02: rocuronium 0.02 mg/kg, Group 0.03: rocuronium 0.03 mg/kg, Group 0.04: rocuronium 0.04 mg/kg, Group 0.05: rocuronium 0.05 mg/kg, Group 0.06: rocuronium 0.06 mg/kg, *P < 0.05 versus Group 0.02, †P < 0.05 versus Group 0.03, ‡P < 0.05 versus Group 0.04, §P < 0.05 versus Group 0.05. P using analysis of variance with the Bonferroni post hoc test. †P = 1 min versus 2 min using one way repeated measures analysis of variance.

**Table 3.** The Incidence and Severity of Fasciculation and Myalgia and Fentanyl Consumption within 24 Hours in Postoperative Patient Controlled Analgesia

| Precurarizing dose (μg) | Number (%) with fasciculation | Fasciculation scores | Number (%) with myalgia | Myalgia scores | Fentanyl (μg) |
|------------------------|-----------------------------|----------------------|-------------------------|--------------|-------------|
| Group 0.02 (n = 20)    | 18 (90%)                    | 2                    | 4                      | 12           | 2           | 9 (45)       | 11 | 7 | 2 | 0 | 0 | 2 | 0 | 752.8 ± 143.6 |
| Group 0.03 (n = 20)    | 15 (75%)                    | 5                    | 8                      | 6            | 1           | 7 (35)       | 13 | 7 | 0 | 0 | 0 | 1 | 0 | 834.5 ± 166.5 |
| Group 0.04 (n = 20)    | 6 (30%)*                    | 14                   | 3                      | 3            | 0           | 4 (20)       | 16 | 4 | 0 | 0 | 0 | 1 | 2 | 802.7 ± 157.8 |
| Group 0.05 (n = 20)    | 4 (25%)*†                   | 15                   | 4                      | 1            | 0           | 4 (20)       | 16 | 4 | 0 | 0 | 0 | 1 | 2 | 754.5 ± 139.8 |
| Group 0.06 (n = 20)    | 4 (20%)*†                   | 16                   | 4                      | 0            | 0           | 2 (10)       | 18 | 2 | 0 | 0 | 0 | 1 | 3 | 786.3 ± 147.9 |
| P                      | < 0.001                     |                      |                        |              |             | 0.072        |     |    |   |   |   |   |   | 0.396 |

Values are presented as numbers (%). of patients and mean ± SD. Group 0.02: rocuronium 0.02 mg/kg, Group 0.03: rocuronium 0.03 mg/kg, Group 0.04: rocuronium 0.04 mg/kg, Group 0.05: rocuronium 0.05 mg/kg, Group 0.06: rocuronium 0.06 mg/kg. Fasciculation scores: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Myalgia scores: 0 = none, 1 = mild, 2 = moderate, 3 = severe. *P < 0.05 versus Group 0.02, †P < 0.05 versus Group 0.03.
curonium 0.05 mg/kg and 0.06 mg/kg at 2 min, respectively.

Awake patients in a TOF ratio below 90% observed at the adductor pollicis complained of the unpleasant experience of swallowing difficulty due to decrease the upper esophageal sphincter tone markedly [13]. It seems possible that the risk of pulmonary aspiration of gastric contents may be increased in patients with a full stomach when the pretreatment of rocuronium is overdosed. When the TOF ratio was 80% in awake patients, forced expiratory vital capacity and forced inspiratory volume in 1 s decreased to 85% of baseline, indicating impaired respiratory muscle strength [14]. In our study, less than 80% of TOF ratio was occurred in 40 and 65% of subjects after precurarizing dose of rocuronium 0.05 mg/kg and 0.06 mg/kg at 2 min, respectively. It seems very possible that awake patients suffered a respiratory difficulty and muscle weakness.

The precurarizing dose of nondepolarizing neuromuscular blockade reduced the neuromuscular blocking potency of succinylcholine and also delayed the onset of succinylcholine [15]. In our study, the onset of succinylcholine was 89 ± 21 s and 95 ± 29 s after precurarizing dose of rocuronium 0.05 mg/kg and 0.06 mg/kg, respectively, which delay the timing of tracheal intubation (e.g. rapid sequence induction). It is therefore suggested, from our results, that rocuronium 0.05 mg/kg and 0.06 mg/kg are not the appropriate dose of rocuronium for the safe and effective precurarization.

A pretreatment with small dose (10% ED95) of rocuronium was recommended for the precurarization in the computer simulation not in the clinical study [4]. In the previous study [8], 0.03 mg/kg rocuronium was recommended for safe and effective precurarizing dose in 3 min before succinylcholine. However, the effect of this dose to prevent fasciculations and postoperative myalgia from succinylcholine was not evaluated and the each subject was too small (n = 12). In our study, precurarization with rocuronium 0.02 mg/kg and 0.03 mg/kg obtained the faster onset of succinylcholine-induced neuromuscular block (55 ± 11 s and 66 ± 15 s), respectively, than other groups. However, this simultaneously maintained the succinylcholine-induced fasciculation (90 and 75%) and myalgia (45 and 35%), respectively (Table 3). It is also suggested that rocuronium 0.02 mg/kg and 0.03 mg/kg are not the appropriate dose of rocuronium for the reduction of the intensity of the fasciculation and myalgia. In the present study, the precurarization with rocuronium 0.04 mg/kg has a disadvantage of increasing the onset time (76 s).

An optimal pretreatment interval of 3 min has been recommended for many commonly used agents such as atracurium and d-tubocurarine [17]. However, such a lengthy interval is not only impractical with busy operating room lists but it also exposes the awake patient to the potentially unpleasant experiences of difficulty in swallowing, breathing and muscle weakness. To avoid these hazards, we chose 2 min of rapid precurarizing time that reduce the possibility to expose the patients to the side effects of the precurarization.

One limitation of this study is that postoperative myalgia was assessed only up to 24 hours. In the previous study, 92% of patients after surgery reported myalgia within 24 hours [18]. Although the incidence of postoperative myalgia was not different between 24 hours and 48 hours [19], it may be accurate to get the results of up to 48 hours.

In conclusion, precurarization with 0.04 mg/kg rocuronium was optimal dose considering that the reduction in the incidence and severity of fasciculation and myalgia with acceptable onset time, and the safe and effective precurarization.

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