Reversal of neuromuscular block with sugammadex: a comparison of the corrugator supercilii and adductor pollicis muscles in a randomized dose–response study

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Background: Neuromuscular monitoring using the corrugator supercilii muscle is associated with a number of challenges. The aim of this study was to assess reversal of a rocuronium-induced neuromuscular blockade with sugammadex according to monitoring either using the corrugator supercilii muscle or the adductor pollicis muscle. We hypothesized that a larger dose of sugammadex would be required to obtain a train-of-four (TOF) ratio of 1.0 with the corrugator supercilii muscle than with the adductor pollicis muscle.

Methods: Forty patients aged 20–60 years and 40 patients aged ≥ 70 years were enrolled. After induction of anesthesia, we recorded the corrugator supercilii muscle response to facial nerve stimulation and the adductor pollicis muscle response to ulnar nerve stimulation using acceleromyography. All patients received 1 mg/kg rocuronium. When the first twitch (T1) of TOF recovered to 10% of control values at the corrugator supercilii, rocuronium infusion was commenced to maintain a T1 of 10% of the control at the corrugator supercilii. Immediately after discontinuation of rocuronium infusion, 2 mg/kg or 4 mg/kg of sugammadex was administered. The time for recovery to a TOF ratio of 1.0 and the number of patients not reaching a TOF ratio of 1.0 by 5 min at each dose and muscle was recorded.

Results: When neuromuscular block at the corrugator supercilii was maintained at a T1 of 10% of control, that at the adductor pollicis was deep (post-tetanic count ≤ 5). Sugammadex 4 mg/kg completely antagonized neuromuscular block at both muscles within 5 min. The time to a TOF ratio of 1.0 at the adductor pollicis was significantly longer in the group ≥ 70 years than the group 20–60 years (mean (SD): 178 (42.8) s vs. 120 (9.4) s, $P < 0.0001$). In contrast, 2 mg/kg sugammadex reversed neuromuscular blockade at the corrugator supercilii but not at the adductor pollicis, with 10 patients in the group 20–60 years and 8 patients in the group ≥ 70 years requiring an additional sugammadex ($P < 0.05$ vs. 4 mg/kg sugammadex).

Conclusion: Sugammadex 4 mg/kg was required to reverse a moderate rocuronium-induced neuromuscular block when the corrugator supercilii muscle is used for monitoring.

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Editorial comment: what this article tells us
Monitoring of neuromuscular function using the corrugator supercilii muscle is possible but recovery occurs faster if the adductor pollicis muscle is used and a larger dose of sugammadex may be needed for reversal of a rocuronium-induced block. Recovery of neuromuscular function was slower in patients over 70 years of age.

The sensitivity of different muscles to non-depolarizing neuromuscular blocking drugs varies.[1] Several differences are seen in the pharmacodynamics of neuromuscular block even between the adductor pollicis muscle and corrugator supercilii muscle,[2–4] which are typical neuromuscular monitoring sites used during clinical anesthesia. In case the ulnar nerve and adductor pollicis unit cannot be used for monitoring because of the patient's body position and location of the surgical field, the facial nerve and corrugator supercilii unit is often easy to access for anesthesiologists and therefore should know the differences in the two muscles. Importantly, the time course of neuromuscular block induced at the corrugator supercilii accurately reflects that at the larynx[5] and diaphragm.[6] Monitoring at the corrugator supercilii may therefore be suitable during maintenance of deeper neuromuscular blockade, to prevent unintentional patient movements and tense abdominal muscles during anesthesia.[7] However, the problem is that the corrugator supercilii recovers earlier than other muscles and the faster recovery of neuromuscular function of the corrugator supercilii cannot simultaneously assure optimum recovery from neuromuscular block induced at the adductor pollicis and upper airway muscles. Our previous study[3] revealed that not only just the blocking profile but also the time required for facilitated recovery with neostigmine from rocuronium-induced neuromuscular block was faster at the corrugator supercilii than at the adductor pollicis. However, the efficacy of sugammadex, now regarded as the reversal agent of choice for rocuronium, at the corrugator supercilii and adductor pollicis has never been compared. So far, sugammadex recommendations are based on the adductor pollicis responses and an optimum dose of sugammadex, of 4 mg/kg for deep rocuronium-induced neuromuscular block or 2 mg/kg for moderate block, can provide reliable recovery to a train-of-four (TOF) ratio of 0.9 at the adductor pollicis in a few minutes;[8–11] however, the doses for the corrugator supercilii have not been assessed. The primary purpose of this study was to determine the reversal dose of sugammadex for the recovery of neuromuscular function when the corrugator supercilii is used for monitoring.

In addition, although it is known that the facilitated recovery from neuromuscular block with sugammadex observed at the adductor pollicis is prolonged in elderly patients,[10] their effects at the corrugator supercilii of the elderly have not been shown. Even minor residual neuromuscular block increases the incidence rate of postoperative pulmonary complications especially in older patients.[12] To prevent postoperative residual neuromuscular block in elderly patients, as the second purpose of this study, it was therefore considered important to compare the recovery property of the corrugator supercilii and adductor pollicis after sugammadex administration and the adequate dosing of sugammadex between younger adult and elderly patients.

We hypothesized that a larger dose of sugammadex would be required to obtain a TOF ratio of 1.0 if monitoring is based on the corrugator supercilii muscle than with the adductor pollicis muscle. We also hypothesized that recovery would be slower in older patients.

Methods

Study design and patient selection

The protocol (protocol number: RK-121214) was approved by the Hospital Ethics Committee on Human Rights in Research (Nihon University Itabashi Hospital, Clinical Research Judging Committee) at December 25, 2012. After registration with the University hospital Medical Information Network (UMIN ID: 000010240), 40 adult (20–60 years of age) and 40 elderly (≥ 70 years) patients consented to participate in

this study. Written informed consent was obtained from all patients after explaining the details of the study by an investigator. Patients were eligible for entry into this study if they were ASA physical status I–II, and were scheduled for elective orthopedic, gynecological, and urological surgery under general anesthesia in Nihon University Itabashi Hospital. None of the patients had neuromuscular, hepatic, or renal disorders, nor were they taking any drug known to interact with neuromuscular blocking agents. Patients whose body mass index was > 30 or < 18.5 kg/m^2 were excluded from the study. The study coordinator enrolled the participants. The 40 patients in each age range were randomized by the chief investigator on the basis of computer-generated randomization numbers to the two study groups of 40 patients each (20 from the group 20–60 years and 20 from the group ≥ 70 years), to receive sugammadex 2 mg/kg or 4 mg/kg. The investigator prepared sugammadex in the operating room according to the randomization. Patients and attending anesthesiologists were blinded to which of the dose of sugammadex.

Study procedures

No premedication was administered. On arrival at the operating room, all patients were placed supine on the bed and routinely monitored with 3-lead ECG, non-invasive blood pressure, and pulse oximetry. Bicarbonated Ringer's solution (5–10 ml/kg/h) was intravenously (i.v) infused in the patient's left forearm via a 20 gauge cannula. General anesthesia was induced with a continuous i.v infusion of remifentanil 0.2–0.3 μg/kg/min, a bolus injection of fentanyl 1–2 μg/kg and propofol 1–2 mg/kg while patients received 100% oxygen through an anesthesia facemask. After loss of consciousness and spontaneous respiration, a laryngeal mask airway was inserted without the aid of neuromuscular blocking drugs. Anesthesia was maintained with an end-tidal sevoflurane concentration of 1.5% and remifentanil 0.2–0.3 μg/kg/min and fentanyl as required. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a BP-608EV™ patient monitor (Omron Colin Inc., Tokyo, Japan). The rectal temperature of the patients was maintained at > 36°C using a warming blanket (Bair Hugger model 750™; Arizant Health care Inc., Eden Prairie, MN, USA).

After a stable depth of anesthesia was obtained, neuromuscular monitoring at the corrugator supercilii and adductor pollicis was concurrently initiated using two sets of acceleromyographs (TOF Watch SX™; Organon Ltd, Dublin, Ireland). The ipsilateral facial nerve at the temporal area or the ulnar nerve at the wrist was stimulated with square-wave stimuli of 0.2 ms duration, which was delivered in a TOF mode at 2 Hz every 15 s. The ulnar nerves were stimulated with a supramaximal current, while the ipsilateral facial nerve was stimulated at a current of 30–35 mA in order to avoid stimulation of other facial muscles and direct stimulation of the corrugator supercilii itself.[1] Skin temperature over the corrugator supercilii or adductor pollicis was recorded every 15 s throughout the experiment using a surface probe, and maintained at > 32°C. All the data obtained at the corrugator supercilii and adductor pollicis were collected on each laptop computer and monitored throughout the study.

After the control TOF stimuli were administered for a minimum of 10 min[13] to stabilize the TOF responses, all the patients received rocuronium 1 mg/kg i.v. Immediately after T1 of the corrugator supercilii muscle recovered to 10% of the control value, a continuous infusion of rocuronium (diluted with physiological saline to 1 mg/ml) was commenced at a rate of 7 μg/kg/min. The infusion rate was adjusted to maintain T1 at 10% of control values at the corrugator supercilii for at least 1 h. All the patients received either sugammadex 2 mg/kg or 4 mg/kg immediately after discontinuation of the rocuronium infusion, according to their randomization. Sugammadex was given as a rapid bolus in a fast running intravenous infusion. If a TOF ratio of 1.0 was not observed within 5 min, an additional 2 mg/kg of sugammadex was administered and the TOF ratio was finally determined at both muscles. In this study, incomplete reversal was defined as the TOF ratio did not reach 1.0 within 5 min after the first dose of sugammadex because recommended 4 mg/kg sugammadex adequately could antagonize rocuronium-induced deep neuromuscular block quantified by 1–2 PTC at the adductor pollicis

in approximately 3 min even in older patients.[10] Until achievement of data collection, anesthesia with sevoflurane and remifentanil were maintained. The laryngeal mask airway was removed when the patient had regained consciousness and respiratory conditions were evaluated by attending anesthesiologist.

The following variables were measured in all patients: onset time (s) from the time of administration of rocuronium to maximum depression of T1; time (min) from the administration of rocuronium to spontaneous recovery of T1 to the first of three consecutive responses at or greater than 10% of the control value at the corrugator supercilii; degree of neuromuscular block at the adductor pollicis (e.g., T1 height, post-tetanic count (PTC)) at the time when the T1 was maintained at 10% of the control value at the corrugator supercilii just before the reversal; the infusion rate (μg/kg/min) of rocuronium required to maintain T1 at 10% of the control value at the corrugator supercilii recorded just before the reversal and the infusion time (min); and the time (s) required for facilitated recovery from the end of injection of sugammadex to a TOF ratio of 1.0 at the two muscles. When three consecutive TOF ratios initially reached or exceeded 1.0, the first TOF ratio of 1.0 was defined as the aimed point of recovery. In case where the TOF ratio did not reach 1.0 within 5 min, the reversal time totally included 5 min after the first dose of sugammadex and the time after additional administration of 2 mg/kg sugammadex.

Statistical analysis

The primary endpoint was time from the end of injection of sugammadex to a TOF ratio of 1.0. It has been reported that the time for reversal of rocuronium-induced deep neuromuscular block at the adductor pollicis to a TOF ratio of 0.9 with sugammadex 2 mg/kg was 3.2 ± 1.5 min.[11] We considered a 50% decrease in the reversal time observed at the corrugator supercilii to be clinically relevant. To detect this difference with $\alpha = 0.05$ and a power of 0.80, it was necessary to include 15 patients in each study group. Considering the risk of dropouts, we enrolled 20 patients in each group and therefore 40 patients in each age group. Data are presented as mean (SD). Statistical analysis was performed using the StatView™ software for Windows (SAS Institute, Cary, NC, USA). The unpaired Student *t*-test or Chi-square test was used for comparisons between the two groups. Differences were reported as mean difference with 95% confidence interval (CI). A *P*-value of < 0.05 was considered statistically significant.

Results

Patients were recruited from April 2013 to July 2014. Two patients in the group ≥ 70 years were excluded from analysis of results because recovery could not be measured in them due to the patient's movement and power battery failure of the acceleromyograph (Fig. 1). Therefore, data from 78 patients could be analyzed. Patients in the groups receiving 2 mg/kg or 4 mg/kg of sugammadex were comparable with respect to age, weight, height, and BMI (Table 1).

Results obtained in the group 20–60 years

Effects of rocuronium

After the administration of a bolus dose of rocuronium 1 mg/kg, complete neuromuscular block was achieved at both muscles. Onset of rocuronium was significantly faster at the corrugator supercilii than at the adductor pollicis (Table 2). When T1 at the corrugator supercilii recovered to 10% of control values, no TOF response was detected at the adductor pollicis in any patients. Duration from the administration of rocuronium to spontaneous recovery of T1 to 10% of the control value at the corrugator supercilii and infusion rate of rocuronium required to maintain T1 at 10% of the control value at the corrugator supercilii did not differ between the patients treated with sugammadex 2 mg/kg or 4 mg/kg. Just before the infusion of rocuronium was terminated, all the PTC data observed at the adductor pollicis indicated deep (PTC ≤ 5) neuromuscular block.

Speed of reversal between the muscles

The time for reversal with 2 mg/kg and 4 mg/kg sugammadex to a TOF ratio of 1.0 was significantly faster at the corrugator supercilii than at the adductor pollicis ($P < 0.0001$, Table 3 and

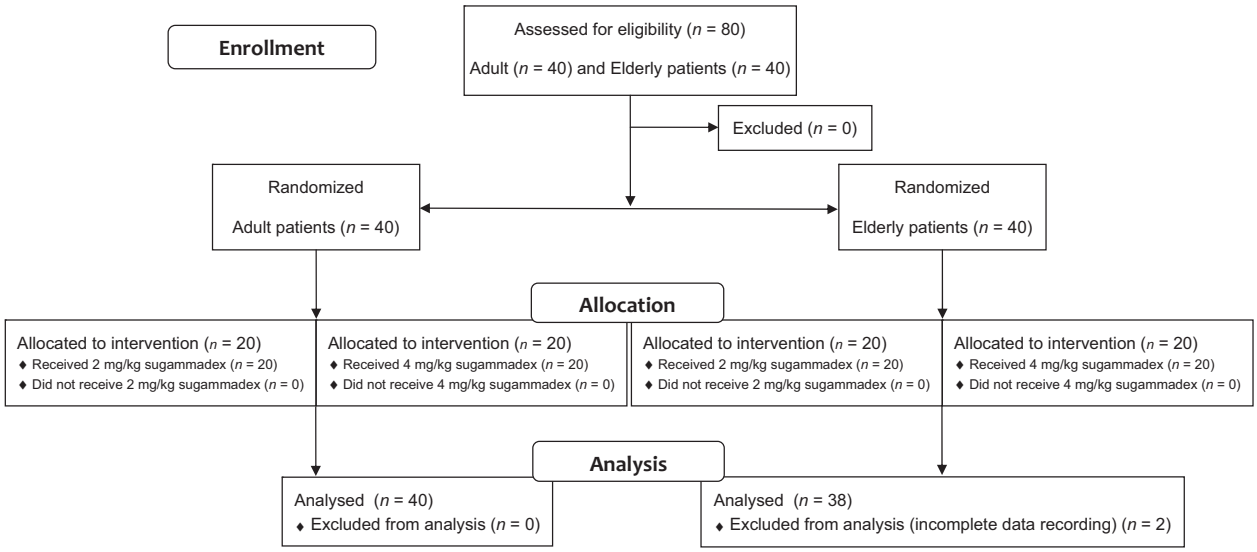

Fig. 1. Trial flow diagram.

Table 1 Patient characteristics.

	Group 20–60 years (n = 40)		Group ≥ 70 years (n = 38)	
Sugammadex	2 mg/kg (n = 20)	4 mg/kg (n = 20)	2 mg/kg (n = 19)	4 mg/kg (n = 19)
Gender (M : F)	8 : 12	7 : 13	7 : 12	7 : 12
Age (years)	44.6 (10.4)	43.1 (10.0)	76.6 (5.5)	78.4 (6.0)
Weight (kg)	55.3 (5.9)	56.9 (6.2)	58.4 (8.4)	58.6 (10.0)
Height (cm)	163.5 (7.6)	161.4 (8.4)	154.3 (7.0)	157.3 (10.3)
BMI (kg/m^2)	22.3 (1.8)	21.7 (1.6)	24.1 (2.7)	23.3 (2.5)

Data are presented as mean (SD).

Fig. 2). However, in the patients treated with 2 mg/kg sugammadex, there was a greater difference in recovery time with a mean difference (95% CI) between the muscles of 160 (102–217) s than in the patients receiving 4 mg/kg where the mean difference (95% CI) between the muscles was 36 (30–41) s.

Dose-related effects of sugamamdex

At the corrugator supercilii, both doses of sugammadex could completely antagonize neuromuscular block and no additional doses were required. In contrast, with the adductor pollicis monitoring, 10 patients (50%, $P < 0.05$ vs. 4 mg/kg sugammadex) treated with 2 mg/kg sugammadex required additional reversal because the TOF ratio did not reach 1.0 [mean: 0.90 (SD: 0.14, range: 0.50–1.0]) within 5 min after the first dose (Fig. 2A). Although recovery of neuromuscular function of the adductor pollicis was significantly slower than that of the corrugator supercilii, 4 mg/kg of sugammadex adequately reversed the deep neuromuscular block induced at the adductor pollicis to a TOF ratio of 1.0 without additional sugammadex doses.

Results obtained in the group ≥ 70 years

Effects of rocuronium

In the patients of the group ≥ 70 years, onset of action of rocuronium and duration from the administration of rocuronium to spontaneous recovery of T1 to 10% of the control value at the

Table 2 Effects of rocuronium-induced neuromuscular block.

	Group 20–60 years (n = 40)	Group ≥ 70 years (n = 38)
Onset at corrugator supercilii (s)	58.6 (9.9)#	84.1 (11.0)#*
Onset at adductor pollicis (s)	70.6 (10.1)	104.1 (10.7)*
Duration to 10% (min)	58.3 (9.0)	89.6 (13.7)*
Infusion rate (μg/kg/min)	7.0 (1.2)	5.0 (1.4)*
PTC	2.6 (1.5)	2.6 (1.7)

Data are presented as mean (SD). #$P < 0.0001$ vs. the adductor pollicis and *$P < 0.0001$ vs. the 20–60 years age group. Duration to 10%: duration of the action after rocuronium 1 mg/kg to recover to 10% of T1 of control at the corrugator supercilii. Infusion rate: infusion rate of rocuronium to maintain 10% of T1 of control at the corrugator supercilii. PTC, post-tetanic count observed at the adductor pollicis when 10% of T1 of control was maintained at the corrugator supercilii.

corrugator supercilii was significantly longer, and the infusion rate of rocuronium required to maintain T1 at 10% of the control value at the corrugator supercilii was significantly smaller than the patients of the group 20–60 years (Table 2). The PTC did not differ between the group 20–60 years and the group ≥ 70 years.

Speed of reversal between the muscles

In the group ≥ 70 years, the time for reversal to a TOF ratio of 1.0 was significantly faster at the corrugator supercilii than at the adductor pollicis ($P < 0.0001$, Table 3 and Fig. 3). However, the patients treated with 2 mg/kg sugammadex had a greater difference in recovery time with a mean difference (95% CI) between the muscles of 176 (103–249) s than those did with 4 mg/kg where the mean difference (95% CI) between the muscles was 82 (64–101) s. No difference in the time for facilitated recovery to a TOF ratio of 1.0 was found according to age at the corrugator supercilii. However, even after a sufficient dose of 4 mg/kg sugammadex, the reversal time observed at the adductor pollicis was significantly slower in the group ≥ 70 years than the group 20–60 years ($P < 0.0001$, Table 3).

Dose-related effects of sugammadex

Within the group ≥ 70 years, 2 mg/kg and 4 mg/kg sugammadex could completely antagonize neuromuscular block at the corrugator supercilii. Because of incomplete recovery of the adductor pollicis judged at 5 min after the first dose [mean TOF ratio: 0.86 (SD: 0.14, range: 0.42–1.0), $P > 0.05$ vs. the group 20–60 years, Figs. 2A and 3A], eight patients ≥ 70 years (42.1%, $P < 0.05$ vs. 4 mg/kg sugammadex) treated with 2 mg/kg sugammadex required additional reversal. Even in the group ≥ 70 years, 4 mg/kg sugammadex could antagonize the deep neuromuscular block induced at the adductor pollicis to a TOF ratio of 1.0.

There was no patient with respiratory distress or upper airway obstruction after the removal of laryngeal mask airway.

Discussion

This study demonstrated that reversal of rocuronium-induced neuromuscular blockade with sugammadex is dose-related and significantly faster at the corrugator supercilii than the adductor pollicis in both the group 20–60 years and the group ≥ 70 years. When T1 was maintained 10% of control at the corrugator supercilii, sugammadex 2 mg/kg was adequate for effective reversal of neuromuscular function of the corrugator supercilii. However, the depth of

Table 3 Time (s) for the reversal to a TOF ratio of 1.0.

	Group 20–60 years (n = 40)		Group ≥ 70 years (n = 38)	
Sugammadex	2 mg/kg (n = 20)	4 mg/kg (n = 20)	2 mg/kg (n = 19)	4 mg/kg (n = 19)
Corrugator supercilii	162.1 (24.0)*	83.3 (12.8)*,#	180.5 (108.8)¶	91.8 (20.7)*,§
Adductor pollicis	328.6 (141.4)	119.9 (9.4) #	365.3 (180.9)	177.6 (42.8)§,†

Data are presented as mean (SD). In cases in which the TOF ratio did not reach 1.0 within 5 min, the reversal time was calculated as the sum of the 5 min after the first dose of sugammadex and the time from additional administration of 2 mg/kg sugammadex until recovery. *$P < 0.0001$ and ¶$P < 0.001$ vs. the adductor pollicis. #$P < 0.0001$ and §$P < 0.001$ vs. 2 mg/kg. †$P < 0.0001$ vs. the 20–60 years age group.

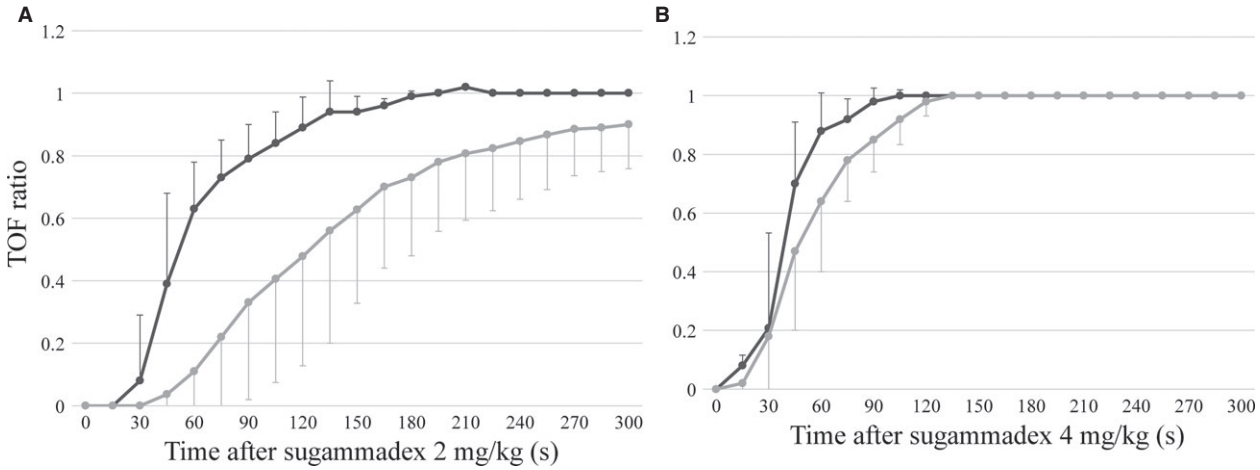

Fig. 2. Time course of facilitated recovery after a bolus of 2 mg/kg (A) and 4 mg/kg (B) sugammadex in the 20–60 y age group. A black line and a gray line show the response of the corrugator supercilii muscle and adductor pollicis muscle, respectively. Data are shown as mean and SD.

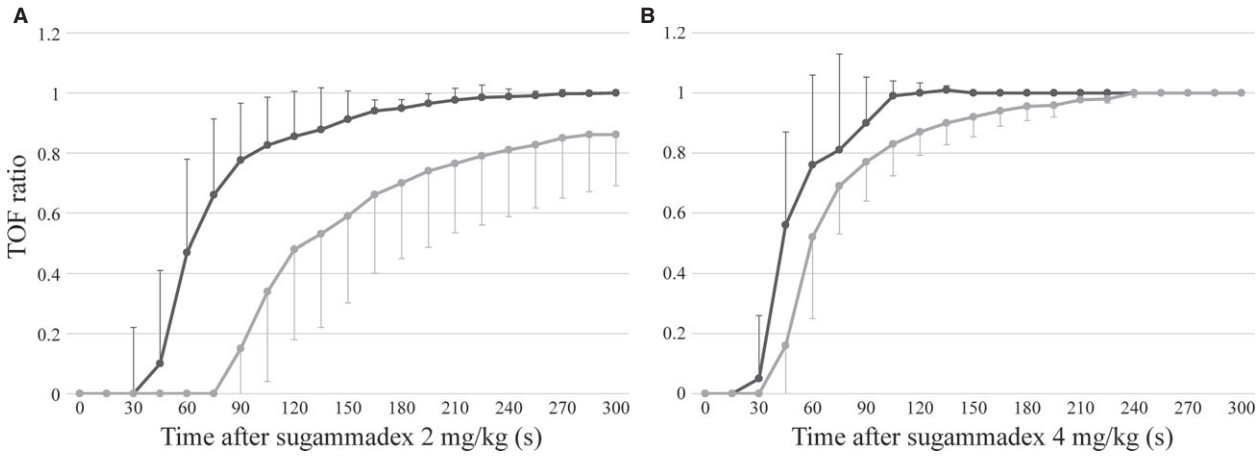

Fig. 3. Time course of facilitated recovery after a bolus of 2 mg/kg (A) and 4 mg/kg (B) sugammadex in the 70 y age group. A black line and a gray line show the response of the corrugator supercilii muscle and adductor pollicis muscle, respectively. Data are shown as mean and SD.

neuromuscular block at the adductor pollicis at this time is probably considerably deep (PTC $\leq$ 5), because of the higher sensitivity of the adductor pollicis to rocuronium, and therefore 4 mg/kg of sugammadex, which is recommended for the reversal of deep neuromuscular block, was required to complete the antagonism irrespective of age. In elderly patients, in particular, it should be remembered that sugammadex facilitation of recovery of neuromuscular function of the adductor pollicis is slower.

As shown in this study, monitoring the depth of moderate neuromuscular block at the corrugator supercilii using simple TOF stimuli and responses may result in the adductor pollicis still being deeply paralyzed and incapable of sufficiently responding to PTC stimulation. Besides, the corrugator supercilii is not appropriate to detect residual paralysis, because its recovery from neuromuscular block is much faster than that of other muscles that are sensitive to non-depolarizing neuromuscular blockade, such as the adductor pollicis and pharyngeal muscles.[14] It is therefore to be noted that a TOF ratio of 1.0 at the corrugator supercilii has less clinical significance because the value does not necessarily ensure adequate recovery of neuromuscular function of the adductor pollicis and upper airway muscles. Although adequate recovery of neuromuscular function should be eventually evaluated at the muscle that is most sensitive to non-depolarizing neuromuscular

blockade, this study may provide useful information for cases in which the corrugator supercilii is used for neuromuscular monitoring. Further, the results also indicate that a bolus dose of 4 mg/kg of sugammadex completely restores neuromuscular function from not only moderate neuromuscular block induced at the corrugator supercilii but also deep block at the adductor pollicis.

Extensively encapsulating the rocuronium molecule into donut-like ring of sugammadex results in a rapid decrease in the plasma concentration of free rocuronium, and induces rocuronium molecules to diffuse from the neuromuscular junction into plasma along the concentration gradient of free rocuronium.[15] Therefore, a faster flux of sugammadex around the target muscle may contribute to a faster onset of its antagonistic action. A previous study[16] demonstrated that there was a significant negative correlation between the time to recover from rocuronium-induced moderate neuromuscular block to a TOF ratio of 0.9 measured at the adductor pollicis and the patient's cardiac output. In this regard, the corrugator supercilii has the advantage of being antagonized faster. Due to its central location, the corrugator supercilii may have enhanced muscle blood flow and shorter circulation time as compared to a muscle supplied by a peripheral vein, such as the adductor pollicis,[17] and consequently, a faster transfer rate of drugs from the plasma to the neuromuscular junction.[18] In addition to different sensitivities of different muscles to neuromuscular blockade, it is likely that differences in pharmacokinetics of sugammadex between the muscles may also be involved in the differential reversibility of sugammadex.

A slower onset and longer duration of action of rocuronium were observed not only at the adductor pollicis but also at the corrugator supercilii, in the group $\geq$ 70 years as compared to the group 20–60 years. The differences can be explained by some age-related pharmacokinetic alterations, such as the decreased muscle blood flow,[19] slower biophase equilibration[20], and reduced plasma clearance of rocuronium.[21] Meanwhile, as can be seen by the fact that the 95% effective doses of rocuronium do not differ between younger adults and the elderly,[22] sensitivity of the endplate to rocuronium remains basically unaffected by aging. However, in the group $\geq$ 70 years in this study, the same depth of neuromuscular block could be maintained by an infusion of 70% of the dose of rocuronium, when compared with the group 20–60 years. To maintain a constant neuromuscular block using an infusion technique, the volume of distribution (Vd) of rocuronium, which is one of the pharmacokinetic factors determining the activity of the drug, should also be considered in addition to the sensitivity of the endplate to rocuronium. The significant decrease in the Vd of rocuronium in the elderly[21] is a reflection of the age-related reduction in body water and cell mass. Therefore, the infusion dose of rocuronium required to maintain a stable depth of neuromuscular block may be lower in the group $\geq$ 70 years than in the group 20–60 years.

Decreased cardiac output and muscle perfusion in older patients results in a slower increase in the plasma concentration of sugammadex, which could also considerably contribute to the slower recovery of neuromuscular function in the group $\geq$ 70 years.[10, 16] Advancing age may have a greater impact on reversibility with sugammadex at the adductor pollicis than at the corrugator supercilii, because the time required to recover to a TOF ratio of 1.0 is more prolonged at the adductor pollicis in the group $\geq$ 70 years. Although the mechanism for this is unclear, it may relate to the fact that functional muscle activity of the corrugator supercilii is maintained even at an older age[23], and, in association with this retained muscle activity, blood perfusion to the corrugator supercilii may also be maintained. It is, therefore, suggested that especially in elderly patients, residual neuromuscular block should be evaluated at the adductor pollicis.

Some limitations should be considered in this study. First, if the reversibility with sugammadex was purely desired to compare between the corrugator supercilii and adductor pollicis, sugammadex should be administered at the same depth of neuromuscular block at each muscle. To achieve the objectives, we should set separate groups monitored at the corrugator supercilii or adductor pollicis. However, the purpose of the present study was to determine an adequate reversal dose of sugammadex for the recovery of neuromuscular function of the two muscles in the same patient.

As the endpoint of this study, we chose a TOF ratio of 1.0, instead of that of 0.9 regarded as gold standard of adequate recovery from neuromuscular block. Although a TOF ratio of 0.9 when measured by mechanomyography at the adductor pollicis is consistently considered adequate recovery of pulmonary and upper airway function, an acceleromyographic TOF ratio of 1.0 should be aimed because acceleromyographic TOF value shows approximately 10% higher than mechanomyography.[24] The secondary limitation is that although a TOF ratio of 1.0 was the goal of the study, upper airway integrity can still be impaired.[25] It is difficult to objectively monitor neuromuscular block induced at the upper airway dilator muscle; therefore, to predict minor residual neuromuscular block, the acceleromyographic TOF value observed at the adductor pollicis should have been normalized. Third, we maintained rocuronium-induced neuromuscular block using a continuous infusion to stabilize and accurately examine the depth of neuromuscular block of the each muscle, and also to make sure that all patients would be at 10% twitch height at the corrugator supercilii at the time of reversal. When compared with an intravenous bolus administration, the infusion technique may reduce redistribution of rocuronium from the neuromuscular junction because the peripheral compartment has become saturated and therefore may bring resistivity to spontaneous recovery[26] and also the reversal with sugammadex, especially in older patients. On the other hand, if bolus doses of rocuronium are given as occurs clinically and when deeper neuromuscular block is observed at the corrugator supercilii, the effect of sugammadex is probably slower and less complete. The relationship between the depth of neuromuscular block evaluated at the corrugator supercilii and the safe dose of sugammadex should be furthermore examined.

In conclusion, the corrugator supercilii recovers earlier than the adductor pollicis, and when one twitch recovers at the corrugator supercilii, the PTC count is usually low at the adductor pollicis. The currently recommended doses of sugammadex for the reversal of rocuronium-induced neuromuscular block are based on the adductor pollicis and therefore, cannot be directly applied to the corrugator supercilii monitoring. Adequate recovery from neuromuscular blockade should be determined at the rocuronium-sensitive muscles, however, when spontaneous recovery from moderate block is observed even with the corrugator supercilii monitoring, 4 mg/kg sugammadex recommended for the depth of 1–2 PTC at the adductor pollicis is adequate to restore neuromuscular function of both the corrugator supercilii and adductor pollicis. In elderly patients, more cautious monitoring on neuromuscular recovery is required because the facilitated recovery with sugammadex is significantly slower than in younger patients.

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