Combined use of Sugammadex and Neostigmine for the Reversal of Rocuronium-Induced Profound Neuromuscular Blockade

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Abstract

Background: Sugammadex is a new reversal agent for nondepolarizing neuromuscular blockade. We conducted the randomized clinical study to compare the recovery between sugammadex alone and combined use of sugammadex and neostigmine.

Methods: Forty adult patients were randomly allocated to Group S (n=20) or Group SN (n=20). General anesthesia was induced and maintained with propofol and remifentanil. The patients were intubated without neuromuscular blockers. After the stabilization of TOF Watch SX® acceleromyography as control, rocuronium 0.6 mg/kg was administered to patients in both groups. The patients in Group S received sugammadex 1.0 mg/kg and those in Group SN received sugammadex 0.5 mg/kg, neostigmine 0.04 mg/kg and atropine 0.02 mg/kg five minutes after rocuronium administration. The cost of reversal and recovery time were measured in both groups.

Results: We analyzed the data of 36 patients (n=18 in each group). The T1/control ratios were significantly higher in Group SN than in group S at 5, 10 and 15minutes after administration of reversal agents. The TOF ratios were significantly higher in Group SN than in group S at 10 and 15minutes after administration of reversal agents. The 90% recovery time of TOF ratio in Group SN was significantly shorter than that in Group S. The cost of reversal was significantly smaller in Group SN than in Group S.

Conclusions: By partially substituting sugammadex with neostigmine, we can attain faster recovery from rocuronium-induced profound neuromuscular blockade.

Keywords: Sugammadex; Neostigmine; Combined use; Reversal from profound neuromuscular blockade

Introduction

Sugammadex is a new reversal agent for nondepolarizing neuromuscular blockade and it is very efficient in reversing any depth of neuromuscular blockade. The mechanism is encapsulation of neuromuscular blocker by sugammadex, and this is a one-to-one molecular interaction. One feature of sugammadex is its quick and dose-related reversal effect on the neuromuscular blockade caused by nondepolararizing neuromuscular blockers [1-4]. When rocuronium induced neuromuscular blockade, the reversal effect is caused within 2-5 min depending on the dose.

A number of reports regarding the comparison between sugammadex and anticholinesterase drugs like neostigmine have been published since sugammadex became used in the clinical setting. Some of them compared the recovery time, and the other compared the economic evaluation between sugammadex and neostigmine [5-9]. However, there have been no reports regarding the combined use of them.

We made the following two hypotheses. First, it is expected that, if a small dose of sugammadex partially reverses profound neuromuscular blockade, the rest of the partial neuromuscular blockade can be reversed with neostigmine because these reversal agents have different mechanism of action. Second, the combined use of these agents may reduce the total cost of reversal because the price of sugammadex is much higher than that of neostigmine (sugammadx 124.3 dollars/ 200 mg vs. neostigmine 3.2 dollars/2 mg in Japan) [10]. Therefore, we conducted a randomized clinical study to compare the

recovery time and cost of reversal from rocuronium-induced profound neuromuscular blockade between sugammadex alone and combined use of neostigmine and sugammadex.

Methods

Approval of the ethics committee of Teikyo University School of Medicine and written informed consent from all the patients were obtained. We recruited forty adult patients (>20 years old), American Society of Anesthesiologists Physical Status 1 who were scheduled for elective surgery under general anesthesia with tracheal intubation. Patients were excluded from the study if they had known difficult airway, had any neuromuscular, cardiac, hepatic, renal or metabolic disorder, received any drug known to influence neuromuscular function or their body mass index was >30 or <20 kg/m². Assuming α of 5% and with 90% power, a sample size of 18 per group was necessary to detect a difference ≥ 0.2 in the mean T1 (1st stimulation in Train-of-Four (TOF))/control or TOF ratio (T4/T1), with a standard deviation

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of approximately 0.2 [11]. Thus, a total of 40 patients were enrolled in this study. A random number table was used to allocate them to Group S (n=20) or Group SN (n=20).

No patient received premedication. An intravenous catheter was inserted into forearm vein and standard anesthesia monitoring (noninvasive blood pressure, electrocardiogram and pulse oximeter) and bispectral index monitoring were established after their arrival in the operating room. General anesthesia was induced with propofol 2 mg/kg and remifentanil 3-4 mcg/kg and the patients were intubated without neuromuscular blockers and mechanically ventilated during the study [12,13]. Anesthesia was maintained with target controlled infusion of propofol at 2.5-5.0 ng/ml and continuous infusion of remifentanil at 0.2-0.5 mcg/kg/min.

Neuromuscular monitoring was carried out according to the international consensus guidelines using TOF Watch SX® acceleromyography at adductor pollicis muscle [14]. The forearm was immobilized and surface skin electrodes were placed over the ulnar nerve at the wrist of the counterlateral arm to noninvasive blood pressure cuff. Before calibration, tetanic stimulation of the ulnar nerve was performed. Then stimulation was switched to TOF mode (consisting of 0.2-ms pulse duration, 2Hz frequency) every 15 seconds. After at least 3minutes of stable twitch response, calibration of the system was performed automatically to find supramaximal stimulation. Recalibration was performed if stimulation was not stable for at least 3 minutes post-calibration. After calibration, the ulnar nerve was stimulated with supramaximal TOF stimulation at 15 seconds intervals. Skin temperature was measured at the site of the neuromuscular monitoring and maintained at 32˚C or higher and core temperature was measured at the bladder or nasopharynx and maintained at 35˚C or higher using heating blankets.

After control stabilization, rocuronium 0.6 mg/kg was administered to patients in both groups. According to the previous studies, neuromuscular blockade of rocuronium is considered to be profound at five minutes after administration [15,16]. The patients in Group S received sugammadex 1.0 mg/kg five minutes after rocuronium

administration. Those in Group SN received sugammadex 0.5 mg/kg and neostigmine 0.04 mg/kg and atropine 0.02 mg/kg five minutes after rocuronium administration (Figure 1). The small dose of sugammadex was intentionally chosen so that sugammadex could partially, not completely, reverse neuromuscular blockade. The recovery time was defined as the time from the administration of reversal agents to the 90% recovery of TOF ratio. The degree of recovery was evaluated by T1/control and TOF ratios. They were measured and recorded every fifteen seconds for forty minutes after the administration of reversal agents.

The cost of reversal was calculated using the following equation;

Cost of reversal in Group S (dollars)=124.3/200* 1* body weight (kg)

Cost of reversal in Group SN (dollars)=(124.3/200* 0.5+3.2/2* 0.04+1.15/0.5* 0.02)* body weight (kg)

The price of atropine was 1.15 dollars/0.5 mg in Japan [10]. All monetary values were originally expressed in Japanese yen, and were converted to the US dollars at a rate of 80 yen=US $1.

When the surgery was completed, all the patients were extubated and observed for at least 30 minutes at the Post-Anesthesia Care Unit (PACU). When they satisfied the PACU discharge criteria, they were transferred to the general hospital wards.
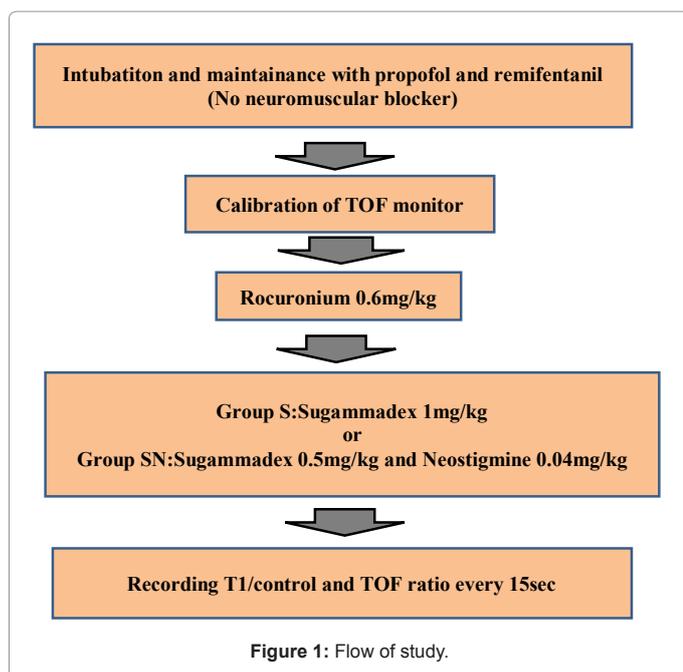
Statistical Analysis

Demographic data were analyzed with chi-square and student t-tests. Statistical analysis of the T1/control and TOF ratios were done using analysis of variance with Bonferroni's adjustment. The time to 90% recovery of TOF ratio and cost of reversal were compared using student t-tests. A p-value less than 0.05 were considered to be statistically significant [11].

Results

Of the forty patients recruited, four were excluded from the study. The reasons for exclusion were;the twitch motion caused by neuromuscular monitoring interfered microscopic surgery (n=1), stable twitch response was not obtained in calibration (n=2) and surgery finished within 40 min after the administration of reversal agent (n=1).

Therefore, we analyzed the data of 36 patients (n=18 in each group). There was no significant difference in demographics between two groups (Table 1). No patient had any response to TOF stimuli at five minutes after rocuronium administration. The T1/control ratios were significantly higher in Group SN at 5, 10 and 15 minutes after administration of reversal agents than those in group S (Group SN vs. S; 0.31 ± 0.28 vs. 0.07 ± 0.14, 0.60 ± 0.29 vs. 0.24 ± 0.21, 0.76 ± 0.24 vs. 0.45 ± 0.25, respectively. p<0.05) (Figure 2). The TOF ratios were significantly higher in Group SN at 10 and 15 minutes after administration of reversal agents than those in group S (Group SN vs.

Figure 1: Flow of study.

Intubatiton and maintainance with propofol and remifentanil (No neuromuscular blocker)

Calibration of TOF monitor

Rocuronium 0.6mg/kg

Group S:Sugammadex 1mg/kg
or
Group SN:Sugammadex 0.5mg/kg and Neostigmine 0.04mg/kg

Recording T1/control and TOF ratio every 15sec

	Group SN	Group S	P-Value
Sex	M13 F5	M10F8	0.29##
Age (yrs)	36.3 ± 14.6	33.9 ± 12.4	0.35#
Height (cm)	165.1 ± 7.7	169.7 ± 9.7	0.46#
Weight (kg)	59.0 ± 8.4	66.5 ± 14.6	0.18#
Stimulation (mA)	44.1 ± 11.2	44.4 ± 12.3	0.79#

Table 1: Demographic data in the two groups. Values are expressed in numbers or means ± SD.

Asterisk: p<0.05.

Figure 2: T1/control after administration of reversal agents. Values are means ± SD.

Asterisk: p<0.05.

Figure 3: TOF ratio after administration of reversal agents. Values are means ± SD.
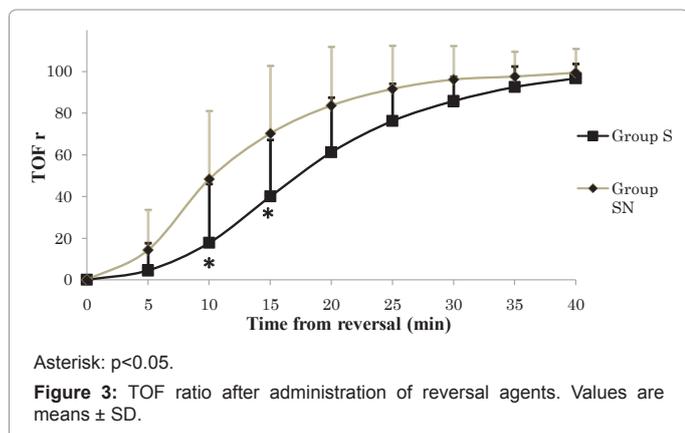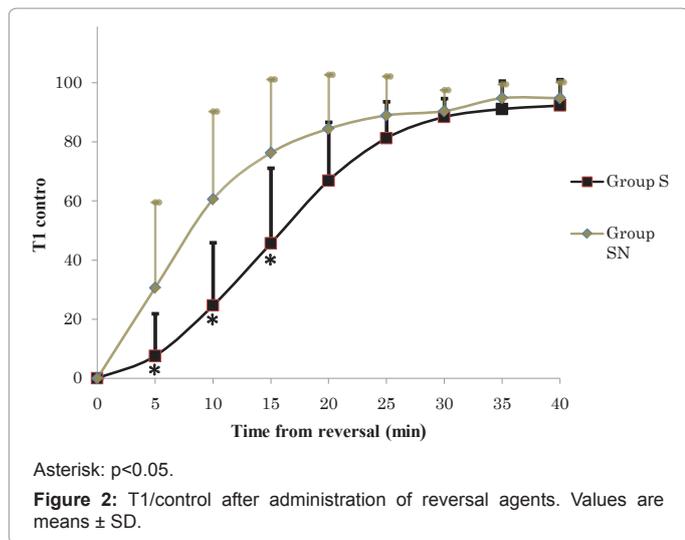
	Group SN	Group S	P-Value
90% recovery time of TOF ratio (min)	18.8 ± 8.9	29.9 ± 7.5	0.00067#
Cost of Reversal (dollar)	24.76 ± 3.48	36.87 ± 6.95	<0.00001#

P values were determined by student t-tests.

Table 2: 90% recovery time of TOF ratio and cost of reversal. Values are expressed in means ± SD.

S; 0.48 ± 0.32 vs. 0.17 ± 0.28, 0.70 ± 0.32 vs. 0.48 ± 0.27, respectively. p<0.05) (Figure 3). The 90% recovery time of TOF ratio in Group SN was significantly shorter than that in Group S (Table 2). The cost of reversal was significantly smaller in Group SN than in Group S (Table 2). No patients had any signs of recurarization, experienced oxygen desaturation <94% or were reintubated in the PACU.

Discussion

In the present study, we demonstrated that the recovery from rocuronium-induced profound neuromuscular blockade was faster with sugammadex and neostigmine combined than with sugammadex alone.

The mechanisms of reversal of nondepolarizing neuromuscular blockade are: increase of acetylcholine release, inhibition of acetylcholine metabolism, metabolism of neuromuscular blocker, and

removal of neuromuscular blocker from acetylcholine receptors [17]. Sugammadex envelops neuromuscular blocker in the blood, increases the concentration gradient of neuromuscular blocker between blood and neuromuscular junction, and removes neuromuscular blocker from the receptors [18]. The mechanism of sugammadex is direct and its onset of action is within few minutes [19,20]. Neostigmine competitively reverses nondepolarizing neuromuscular blockade by inhibiting acetylcholinesterase and increasing acetylcholine concentration at neuromuscular junction. The mechanism of neostigmine is indirect and its onset of action is over seven minutes [21]. Neostigmine 0.06-0.08 mg/kg inhibits over 90% acetylcholinestrerase activity and has a ceiling effect; increasing the dose of neostigmine does not make reversal faster [6]. Neostigmine alone is unable to reverse profound neuromuscular blockade when T1/T4 is zero [22].

We speculate that the mechanism of reversal in Group SN is as follows. First, sugammadex 0.5 mg/kg partially reverses profound neuromuscular block within few minutes. Then, neostigmine reverses the rest of partial neuromuscular blockade. Bevan et al. [22] demonstrated that it took 19 minutes for neostigmine 0.07 mg/kg to reverse neuromuscular blockade to TOF ratio 90% when T1/control is 1%. This result is similar to the time to 90% recovery of TOF ratio in Group SN in our present study. Therefore, it is speculated that sugammadex 0.5 mg/kg reversed neuromuscular blockade to T1/control 1% before neostigmine reversed to TOF ratio 90%.

We measured the time to 90% recovery of TOF ratio because it is required for extubation. In the past, 70% recovery was considered sufficient for extubation [23]. However, the recent studies have shown that the reactivity of carotid body is low and risk of aspiration is high due to skeletal muscles dysfunction in larynx and upper esophagus when the recovery of TOF ratio is 70% [24,25]. Our results suggest that patients can be extubated earlier when sugammadex and neostigmine are used together than when sugammadex is administered alone.

The price of sugammadex is approximately 35 times as expensive as that of neostigmine in Japan [10]. There has been no other choice than sugammadex when the reversal of profound neuromuscular blockade is required [22]. The present study demonstrated that the combined use of neostigmine and sugammadex significantly reduced the cost of reversal of profound neuromuscular blockade by about 33%. However, these numbers may differ in different countries and different pharmaceutical markets [9]. Moreover, sugammadex is currently sold in a 200 mg vial in Japan, and is not to be divided among patients. Unless a smaller dose vial is available, the cost reduction will not be realized.

There are some limitations in the present study. First, we did not measure the profound neuromuscular blockade using post-tetanic contraction before administering reversal agents. However, the onset of rocuronium 0.6 mg/kg is about 89 seconds [15]. Bayakara et al. [16] showed that it took 15 minutes after rocuronium 0.5 mg/kg was administered before post-tetanic contraction appears. Therefore, the neuromuscular blockade was considered profound when reversal agents were administered in our study. Second, we did not observe natural recovery of rocuronium as a control group. However, Bevan et al. showed that natural recovery time of rocuronium is 54 minutes under nitrous oxide-oxygen-propofol anesthesia which is much longer than that of our study [22]. Therefore, the reversal agents in our study promoted the recovery from rocuronium-induced profound neuromuscular blockade.

In conclusion, by partially substituting sugammadex with

neostigmine, we can attain faster recovery from rocuronium-induced profound neuromuscular blockade.

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