Reversal of Deep Effect of Rocuronium by Sugammadex or Neostigmine after Abdominal Laparoscopic Surgery: A Single Center Experience in Vietnam

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Abstract

BACKGROUND: Using sugammadex allows to quickly reverse deep neuromuscular blockade with rocuronium in laparoscopic surgery, which results in great benefits during and after surgery by minimizing the problem of postoperative residual curarization.

AIM: The aims of this study are comparing the efficacy of reversing neuromuscular blockade between sugammadex and neostigmine and evaluating its unwanted effects after laparoscopic abdominal surgery.

METHODS: Subject of this prospective clinical comparative trial was patients who underwent abdominal laparoscopic surgery at 103 Military Hospital from October 2017 to October 2018. Eighty-four patients suffering from abdominal laparoscopic surgery under deep neuromuscular blockade were enrolled and divided randomly into two groups with 42 patients in each: Group N used neostigmine for neuromuscular blockade reversal and Group S applied sugammadex. At the end of surgery, neuromuscular blockade was reversed with either sugammadex or neostigmine.

RESULTS: The reversal time to achieve train-of-four ratio >0.9 in the sugammadex group was 2.42 ± 0.58 min, which was shorter than in the neostigmine group (11.83 ± 2.19 min) (p < 0.05). The time until extubation in the sugammadex group was 3.69 ± 0.67 min, which was shorter than in the neostigmine group 11.90 ± 2.22 min (p < 0.05). Reversal with sugammadex resulted in statistical significance of less sputum production (0% vs. 11.9%), dry mouth (0% vs. 28.57%), headache (2.38% vs. 7.14%), and nausea (4.76% vs. 14.28%) compared with neostigmine. However, 26.19% of patients in the neostigmine group presented bradycardia, whereas the concurrent administration of atropine in the neostigmine group resulted in increased heart rate.

CONCLUSION: Sugammadex reversed neuromuscular blockade more rapidly and effectively than neostigmine in abdominal laparoscopic surgeries. The unwanted effects of sugammadex group were fewer than neostigmine group.

Introduction

Laparoscopic surgery, particularly laparoscopic abdominal surgery, has a large number of advantages, such as improving early postoperative ambulation as well as reducing complications after surgery. General anesthesia is the most commonly applied method for laparoscopic surgery. However, the increased intra-abdominal pressure brings in some limitations because of relating to hemodynamic effects.

Neuromuscular blockade plays a crucial role in facilitating intubation and optimizing surgical conditions during laparoscopic procedures [1]. However, if neuromuscular blockade, especially deep relaxation, is used to facilitate surgical visualization during laparoscopic surgeries, residual neuromuscular blockade after surgery is a matter of concern. Residual neuromuscular blockade may precipitate adverse respiratory events as a consequence of reduced minute ventilation or impaired protective airway reflexes. An accurate and complete post-operative assessment of residual neuromuscular blockade as well as the reversal of that blockade (especially deep relaxation) plays an important role. Therefore, the use of acetylcholinesterase inhibitors (AChEI) or sugammadex has been recommended to recover from neuromuscular blockade after surgery [2]. Using sugammadex to reverse neuromuscular blockade can avoid cardiovascular and respiratory effects resulting from AChEIs [3]. Reversing deep neuromuscular blockade by sugammadex after

abdominal laparoscopic surgery results in great benefits during and after surgery by minimizing the problem of postoperative residual curarization (PORC). This problem is still quite new in Vietnam.

The aims of this study are comparing the efficacy and unwanted effect of the reversal of neuromuscular blockade with sugammadex and neostigmine after laparoscopic abdominal surgery in Vietnamese patients. The primary outcomes included train-of-four ratio (TOF) ratio (the ratio of T4/T1) at the point of time from T0 to T14; duration to achieved TOF ratio = 0.5, 0.7, 0.9, and 1; and time of extubation and the incidence of side effects (secretion, dry mouth, headache, nausea, and bradycardia).

Subjects and Methods

Subjects in this study were patients who underwent abdominal laparoscopic surgery for cholecystectomy, gastrectomy, hepatectomy, and pancreatoduodenectomy at Military Hospital 103 between October 2017 and October 2018. Exclusion criteria included: The age under 18 or above 70 years old, liver failure, kidney failure, allergy to rocuronium, neostigmine or sugammadex, history of epilepsy, mental illness and communication difficulties, coexisting neurological complication of diabetes or neuropathy, and lack of consent. Patients were also excluded if they suffered allergic reactions to any of the drugs or serious surgical complications. In this study, 120 patients were enrolled and 36 patients were excluded from the study. All patients were signed written informed consent and this study was carried out in accordance with the principles of the Declaration of Helsinki.

In this prospective clinical comparative trial, we used the formula: $n = 2C/(ES)^2$ to calculate sample size with accepting an α error = 0.01, β error = 0.05, power test = 0.95 (95%), C = 19.84 (consulted the table with a power test of 95%). ES is the effect size calculated according to Glass formula:

$$ES = \overline{X}_1 - \overline{X}_2/SD_{control}$$

$\overline{X}_1$ and $\overline{X}_2$ are the mean values of controlled and interventional group; SD control is the standard deviation of the controlled group estimated, according to the previous studies.

According to Gulec *et al.*, the duration of neuromuscular blockade reversal by neostigmine and sugammadex was 269.1 ± 135.21 s and 130.37 ± 167.29 s, respectively [4]. With that values we had n = (2 × 19.84)/(1.026 × 1.026) = 37.7. Thus, there were at least 38 cases in each group. In our study, 120 patients were collected and 36 patients were excluded from the study. There were 84 cases left who were divided into two groups: Group N (reversed neuromuscular blockade with neostigmine 40 µg/kg and atropine 10 µg/kg, n = 42) and Group S (reversed neuromuscular blockade with sugammadex 2 mg/kg, n = 42).

Study protocol

Patients were evaluated before surgery following standard practices to ensure they were suitable and appropriately optimized for the planned procedure. In the operating room, an 18-gauge intravenous cannula was inserted and standard monitoring (non-invasive blood pressure, pulse oximeter, electrocardiography, and capnography) was applied. Neuromuscular function was started monitoring from induction with TOFscan® (IDMed) and the tridimensional sensor pup on the adductor pollicis muscle to detect any movements. Induction anesthesia was started with the dose of fentanyl 3 µg/kg, propofol 2–2.5 mg/kg and rocuronium 0.6 mg/kg. Tracheal intubation was implemented when >95% twitch depression was confirmed. Mechanical ventilation was maintained with 8–10 ml/kg tidal volumes and a respiratory rate of 12–14 cycles/min. Other targeted parameters were peak airway pressures of 12–16 cm H_2O and $EtCO_2$ of 35–40 mmHg with a fresh gas flow of 1.2–2 L/min. During abdominal insufflation, these parameters were adjusted to keep $EtCO_2$ <40 mmHg and airway pressure <30 cm H_2O. The CO_2 insufflation pump was set at 10 mmHg level.

All patients were performed general anesthesia and maintained with sevoflurane. Rocuronium induction dose was 0.6 mg/kg for endotracheal intubation and additional doses of 0.15 mg/kg were employed when the TOF showed ≥1 twitch (If the estimated time from the point of injection to the point of abdominal closure was <20 min, the rocuronium was not reused). Neuromuscular blockade monitor was applied base on Good Clinical Research Practice guidelines [5].

TOFscan® (IDMed) monitoring helps to collect automatically train-of-four data. According to the guideline mentioned above, the onset of neuromuscular blockade was defined as the time from the starting of intravenous injection of rocuronium to achieving twitch depression >95%. Then, intubation conditions were assessed with the scoring system as described by the Good Clinical Research Practice guidelines [5]. TOF ratio was noted after intubation immediately; the post-tetanic count (PTC) was also counted after obtaining TOF ratio. The TOF ratio was monitored every 15 s, and PTC was every 3 min to remain a PTC count of 1–2 to have a deep blockade. A repeated dose of rocuronium 0.15 mg/kg was administered to keep TOF and PTC in targets. The moderate blockade was defined as a level of neuromuscular block with TOF-count ≥1, deep blockade was defined as the presence of PTC count ≥ 1 and TOF count =0, and the intense blockade was defined as no response to any pattern of nerve stimulation (PTC = 0). Mechanical ventilation was adjusted to keep the end-tidal carbon dioxide concentration between 35

and 40 mmHg. Body temperature was maintained at the normal range.

When the surgical procedure completed, neuromuscular blockade was reversed by either sugammadex 2 mg/kg or neostigmine 40 µg/kg combined with atropine 10 µg/kg when TOF reached 2. Until the TOF ratio ≥0.9 and other extubation criteria were met such as normal mental; normal skin and mucous; cough reflex recovery; and respiratory: Spontaneous breath of 10–30 times/min; Vt >5 ml/kg; circulatory: Systolic blood pressure ≥90 mmHg; heart rate ≥60 beats/min; body temperature ≥35°C; and no surgical complications, patients' tracheal tube was extubated in the operating room. The level of neuromuscular blockade just before injecting the reversal agents, and the recovery time (which was defined as the time from injecting the reversal agents to achieving a TOF ratio of 0.9) was recorded.

Before discharging from the recovery room, all symptoms and signs of residual curarization after an operation such as episode of hypoxia (SpO$_2$ <95%), ability or inability to sustain head-lifting for >5 s, and presence of diplopia were assessed. The primary outcomes included TOF ratio (the ratio of T4/T1) at the point of time from T0 to T14; duration to achieved TOF ratio = 0.5, 0.7, 0.9, and 1; and time of extubation and the incidence of side effects (secretion, dry mouth, headache, nausea, and bradycardia). Baseline characteristics (age, weight, height, and ASA), classification of surgery, duration of surgery, duration of anesthesia, onset time, and recovery time of neuromuscular blockade (time from the last dose of rocuronium until the patient was transferred to the recovery room), and the total doses of rocuronium, neostigmine, atropine, and sugammadex were recorded.

Characteristics of reversing neuromuscular blockade were measured at 15 time points T0, T1, T2, T3, T4, T5, T6, T7, T8, T9, T10, T11, T12, T13, and T14 as 0 s, 15 s, and 30 s; 1 min, 2 min, 3 min, 4 min, 5 min, 6 min, 8 min, 10 min, and 20 min; and 1 h, 12 h, and 24 h after extubation. At the same times, other data including temperature, respiratory rate, SpO$_2$, heart rate, blood pressure, muscle recurarization (muscle recurarization was defined as a decrease in TOF <0.9 recorded on a TOF scan at any time after the TOF score was ≥0.9) and unwanted effects including nausea/vomiting, secretion, bradycardia, and dry mouth, were also recorded.

Statistical analysis

The data were collected, analyzed, and processed by medical statistics using SPSS 22.0 software. Quantitative variables were described as the mean ± standard deviation. Discrete variables were described in percentages. Student's t-test was used to make a quantitative comparison of averages between two-independent distribution groups; ANOVA test was used when comparing mean values from different groups. The differences between two groups were deemed statistically significant when p < 0.05. The comparisons between two groups were used to test for the Chi-square. Mann–Whitney test was used in a comparison of non-distributed variables between two groups.

Ethical considerations

This study was approved by the Scientific Council of Military Medical University and 103 Military hospitals. The study details were explained to patients and informed consent obtained before the procedure. Sugammadex and neostigmine were used in Vietnam with the permission of the Ministry of Health.

Results

The study was carried out on 84 patients who were performed abdominal laparoscopic surgery and randomly divided into two groups. Baseline characteristics were similar in both groups (Table 1: Patients demographic and Table 2: Clinical data).

Table 1: Patients demographics

Group	Group N (n=42)	Group S (n=42)	p-value
Age (years)	56.31 ± 12.97	59.64 ± 14.68	0.273
Gender (male/female)	42.9/57.1	33.3/66.7	
Height (cm)	159.83 ± 7.85	161.38 ± 8.00	0.372
Weight (kg)	54.19 ± 10.49	55.73 ± 10.82	0.509
BMI (kg/m²)	21.13 ± 3.09	21.27 ± 2.85	0.829
ASA			
I/II/III/IV	0/41/1/0	0/39/3/0	
Coexisting diseases			
Hypertension	6 (14.3)	6 (14.3)	
Diabetes	0 (0)	1 (2.4)	0.233
COPD	1 (2.4)	1 (2.4)	
Valvular heart disease	0 (0)	1 (2.4)	
No disease	35 (83.3)	33 (78.5)	

Results: mean±SD; analysis by Student's t-test

The mean TOF value of the sugammadex group was higher than that of the neostigmine group at all times from 1 to 20 min after reversing neuromuscular blockade. The differences were statistically significant with p < 0.05. (Table 3: TOF ratio after reversing neuromuscular blockade).

Table 2: Clinical data

Group	Group N (n=42)	Group S (n=42)	p-value
Duration of surgery (min)	155.17 ± 50.02	174.52 ± 67.33	0.138
Duration of anesthesia (min)	167.52 ± 51.33	186.69 ± 67.40	0.146
Duration between the last rocuronium injection and the end of surgery (min)	30.88 ± 9.88	30.40 ± 9.22	0.818
Fentanyl (µg)	416.67 ± 85.30	403.57 ± 93.96	0.505
Rocuronium (mg)	100.83 ± 18.84	102.62 ± 17.05	0.649
Number of rocuronium doses	3.93 ± 0.81	3.69 ± 0.95	0.216
Types of surgery			
Gastrectomy	13 (31.1)	13 (31.1)	
Cholecystectomy	10 (23.8)	11 (26.2)	
Hepatectomy	0 (0)	2 (4.8)	0.639
Pancreatoduodenoectomy	3 (7.1)	3 (7.1)	
Colonoscopy	15 (35.7)	12 (28.6)	
Splenectomy	1 (2.4)	1 (2.4)	

Results: mean±SD; analysis by Student's t-test

Table 3: TOF ratio after reversing neuromuscular blockade

Time	Group		
	Group N (n=42)	Group S (n=42)	p-value
T0 (%)	0	0	
T1 (%)	0	0.50 ± 3.24	0.323
T2 (%)	0.36 ± 2.31	3.88 ± 9.45	0.021*
T3 (%)	1.17 ± 5.28	29.73 ± 20.82	<0.001*
T4 (%)	2.36 ± 8.91	71.59 ± 20.46	<0.001*
T5 (%)	11.95 ± 17.33	97.07 ± 7.36	<0.001*
T6 (%)	25.95 ± 13.09	99.52 ± 3.09	<0.001*
T7 (%)	41.52 ± 12.87	100	<0.001*
T8 (%)	55.59 ± 8.93	100	<0.001*
T9 (%)	73.21 ± 7.84	100	<0.001*
T10 (%)	83.88 ± 6.69	100	<0.001*
T11 (%)	98.69 ± 2.38	100	<0.001*
T12 (%)	100	100	
T13 (%)	100	100	
T14 (%)	100	100	

*p<0.05 analysis by Student's t-test. TOF: Train-of-four ratio.

The duration to achieve TOF value ≥ 0.5, TOF ≥ 0.7, TOF ≥ 0.9, and TOF = 1 was significantly shorter in Group S than in Group N with $p < 0.05$. The recovery time to achieve the TOF ratio > 0.9 in the sugammadex group was 2.42 ± 0.58 min, which was significantly shorter than in the neostigmine group (11.83 ± 2.19 min) ($p < 0.05$). (Table 4: Results of neuromuscular rehabilitation after surgery).

Table 4: Results of neuromuscular rehabilitation after surgery

TOF	Group		
	Group N (n=42)	Group S (n=42)	p-value
TOF=0.5 (min)	5.62 ± 1.01	1.33 ± 0.38	<0.001*
TOF = 0.7 (min)	7.47 ± 0.95	1.76 ± 0.42	<0.001*
TOF = 0.9 (min)	11.83 ± 2.19	2.42 ± 0.58	<0.001*
TOF = 1 (min)	17.51 ± 3.18	2.92 ± 0.73	<0.001*

*p<0.001 analysis by Student's t-test. TOF: Train-of-four ratio.

The time until extubation in the sugammadex group was 3.69 ± 0.67 min, which was shorter than in the neostigmine group 11.90 ± 2.22 min ($p < 0.05$). (Table 5: The variables related to reversing neuromuscular blockade).

Table 5: The variables related to reversing neuromuscular blockade

Variables	Group		
	Group N (n=42)	Group S (n=42)	p-value
Time extubation (minutes)	11.90 ± 2.22	3.69 ± 0.67	0.001*
Temperature at reversal neuromuscular blockade (°C)	36.49 ± 0.10	36.49 ± 0.12	0.806
Temperature at extubation (°C)	36.51 ± 0.14	36.51 ± 0.13	0.841
Respiratory rate before extubating (rate/min)	16.67 ± 1.28	16.74 ± 1.39	0.545
Respiratory rate after extubating (rate/min)	16.97 ± 1.27	16.83 ± 0.93	0.592

*p<0.05 analysis by Student's t-test.

Regarding unwanted effects, the heart rate and blood pressure did not significantly change in the sugammadex group. The heart rate was recorded to increase in the group using neostigmine and atropine. There were 2.38% of patients suffering from headache in Group S. Meanwhile, in Group N, 11.90% of patients increased sputum production, 28.57% of patients suffered from dry mouth symptoms, 7.14% of patients had headaches, and 14.28% of patients experienced nausea symptoms. There was a significant difference between sputum production, dry mouth, and nausea symptoms between the two groups with $p < 0.05$. (Table 6: Unwanted effects).

Table 6: Unwanted effects

Unwanted effects	Group		
	Group S (n=42) n (%)	Group N (n=42) n (%)	p-value
Secretion	0	5 (11.90)	0.045*
Dry mouth	0	12 (28.57)	<0.001*
Headache	1 (2.38)	3 (7.14)	0.616
Nausea	2 (4.76)	6 (14.28)	0.265
Bradycardia	0 (0)	11 (26.19)	<0.001*

*p<0.05 analysis by Student's t test.

Discussion

An ideal neuromuscular blocking drug should have characteristics such as quick onset, short duration of action, few muscarinic unwanted effects, no accumulation in the body, and especially the ability to rapidly recover neuromuscular function after general anesthesia with deep neuromuscular blockade. With the introduction of sugammadex, this new reversal agent allows rapid and complete reversal of neuromuscular blockade induced by rocuronium.

In our study, patients' age was higher than those in the study by Wu [6]. In elderly patients, anesthesiologists must consider patients' conditions such as reduced physiological function, weakness, and coexisting diseases that affect the recovery of the respiratory muscles function. Elderly patients were at greater risk of PORC, with a longer duration of neuromuscular rehabilitation than younger patients [7]. Therefore, the assessment of the PORC, as well as the relaxation after general anesthesia (especially deep relaxation), plays a crucial role in the success of the surgery and patient safety.

Prolonged operative duration would be affected by the accumulation of rocuronium, the reversal of neuromuscular blockade and residual curarization after surgery, especially in elderly patients [8]. The results in this study had a longer duration of surgery than those of Gulec *et al*., in which operation time was 105.47 ± 53.38 min [9]. The reason behind this is that our study included both gastric and colon surgeries which usually require longer operative times. Besides, the total dose of drugs was higher than that of Sacan *et al*. [4]. In our study, we used rocuronium at a dose of 0.6 mg/kg body weight for endotracheal intubation. Elderly patients accounted for a large proportion in our study, who have a high rate of PORC due to functional impairment [10], [11]. The dose of sugammadex 2 mg/kg or neostigmine 40 μg/kg plus atropine 10 μg/kg to reverse neuromuscular blockade when the second stimulus appeared in the TOF stimulus four series was used. This dose was similar to other studies on residual assessment and restoration [12], [13], [14].

Choosing the time and dose to administer muscle relaxant, selecting a method for reversing neuromuscular blockade, and evaluating the PORC, are very important to ensure safety and avoid complications after surgery but which is the best

TOF-count to reverse neuromuscular blockade with neostigmine still is controversial. The results showed that the recovery time of patients receiving a dose of 2 mg/kg sugammadex was significantly faster than those receiving a dose of 40 µg/kg neostigmine and atropine 10 µg/kg. The results were similar to the study of Geldner *et al*. on laparoscopic abdominal surgery [15] and Jain and Gandhi on laparoscopic surgery [16]. Studying on 60 elderly patients undergoing cholecystectomy, Yazar *et al*. showed that as age increased, the time from injecting of sugammadex to obtaining TOF ratio of 0.9 was more than 3.27 min [17]. Slower mean recovery time in the elderly than in young patients may be a reflection of decreased blood flow to the muscles or an increased volume of distribution in elderly patients [18], [19]. Although the recovery time of the TOF of sugammadex in elderly patients was longer than in the younger patients, there was no statistically significant difference. Sugammadex rapidly reversed neuromuscular blockade induced by rocuronium in all age groups, including the elderly [13] and especially showed efficacy in the reversal of moderate and deep neuromuscular blockade [20].

Average time until endotracheal extubation was similar to the result of the study of Gulec *et al*. when comparing the effect of sugammadex and neostigmine in reversing rocuronium under general anesthesia with desflurane [9].

Neostigmine is a neuromuscular blockade reversal agent commonly used in clinical practice. It contains a carbamate group that inhibits acetylcholinesterase by forming a reversible covalent bond to carbamylate the enzyme. Neostigmine agents could not reverse neuromuscular blockade when the blockade is deep. The discovery of cyclodextrin (sugammadex), which effectively reverses deep muscle relaxation of non-depolarizing muscle relaxants, was very valuable. Sugammadex not only effectively reversed muscle relaxation but also shortened the onset time, time until extubation, and recovery time [21].

The time until extubation criteria were met after reversing neuromuscular blockade in Group S was significantly faster than that in Froup N. This was demonstrated by the faster recovery time of TOF in Group S than that of Group N. The temperature, respiratory rate, capillary oxygen saturation, and SpO_2 were not significantly different. The heart rate slightly increased in the N group (neostigmine and atropine) but did not show statistical significance. Mean blood pressure was also no statistically significant different between the two groups. These results were in line with other research [14], [22].

Neither group in this study included patients who suffered from cardiac arrhythmias, bronchospasm, or allergy to neostigmine or sugammadex. Most unwanted effects were bradycardia, increased sputum, dry mouth, headache, nausea, and vomiting. The proportion of patients suffering from these unwanted effects was similar to other studies [23], [24]. There is still no evidence in the literature to blame headache and nausea for using sugammadex or neostigmine as well because there were many affected factors. That is why it needs to have a further study for categorizing this regarding.

Conclusion

Reversal of rocuronium in 84 Vietnamese patients who underwent abdominal laparoscopic surgery by a dose of 2 mg/kg of sugammadex or 40 µg/kg of neostigmine combined with 10 µg/kg of atropine showed that sugammadex reversed neuromuscular blockade more rapidly and effectively than neostigmine. The unwanted effects of using sugammadex were fewer than neostigmine.

Acknowledgments

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