ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 29(2); April 2025 DOI: 10.35975/apic.v29i2.2703

ORIGINAL RESEARCH GENERAL ANESTHESIA

Effects of sugammadex on deep neuromuscular blockade reversal in laparoscopic colorectal resection: a prospective observational study

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ABSTRACT

Background & objective: Sugammadex can provide a rapid recovery from deep neuromuscular blockade induced by aminosteroid non-depolarizing paralytics and has recently been recommended as a routine reversal agent for neuromuscular blockade induced by rocuronium or vecuronium. This study aims to investigate the efficacy and safety of sugammadex on the reversal of rocuronium-induced deep neuromuscular blockade in patients undergoing laparoscopic colorectal resection.

Methodology: This was a prospective observational study on 59 patients who had scheduled laparoscopic colorectal resection surgery in a national teaching hospital in Vietnam. The primary outcome was the time to reach a train-of-four ratio of 0.9. Secondary outcomes included the incidence of deep neuromuscular blockade at the end of the surgery and the incidence of residual neuromuscular blockade in the post-anesthesia care unit (PACU).

Results: The average time to reach a train-of-four (TOF) ratio of 0.9 was 4.0 min (ranging from 1.5 to 8.9 min). It took 4.2 min and 3.7 min to fully recover of neuromuscular function in the 4 mg/kg and the 2 mg/kg groups, respectively. At the end of the surgery, 62.7% of patients remained under a deep level of neuromuscular blockade. There was no incidence of residual paralysis recorded in the PACU. Older age and higher ASA classification appeared to be associated with prolonged time to reach a TOF ratio of 0.9 following reversal by sugammadex.

Conclusions: Sugammadex provided a rapid recovery from deep blockade induced by rocuronium in laparoscopic colorectal resection patients and there was no event of residual blockade in the PACU.

Keywords: Sugammadex; Deep Neuromuscular Blockade; Laparoscopic Colorectal Resection; Residual Neuromuscular Blockade

Citation: Phan VTN, Nguyen DT, Phi HT. Effects of sugammadex on deep neuromuscular blockade reversal in laparoscopic colorectal resection: a prospective observational study. Anaesth. pain intensive care 2025;29(2):194-201. **DOI:** 10.35975/apic.v29i2.2703

Received: July 30, 2024; **Reviewed:** October 26, 2024; **Accepted:** February 04, 2025

1. INTRODUCTION

The use of intermediate-acting neuromuscular blocking agents such as rocuronium and vecuronium still pose a possible threat of residual neuromuscular blockade, which has been proved to be dose-dependent and associated with postoperative critical respiratory events and delayed recovery of patients.[1,2] Despite many developments regarding neuromuscular management including new agents with improved pharmacokinetic characteristics and the introduction of neuromuscular monitoring devices added to clinical observations, the risk of residual paralysis persists and is usually under-detected.[3,4]

In the recent years, deep neuromuscular blockade has been used routinely in laparoscopic surgeries including

colorectal surgeries, thanks to its ability to provide better surgical conditions and facilitate the use of low-pressure pneumoperitoneum.[5] The wide application of deep neuromuscular blockade in laparoscopic surgery has led to the need for a rapid and effective reversal agent to reduce the incidence of postoperative residual paralysis and complications, as well as to shorten operative turnover time. Sugammadex, by far, is considered to be an ideal reversal agent that could satisfy those requirements thanks to its rapid onset of action, better tolerance, and better safety profile in comparison to neostigmine in many randomized controlled trials.[6-8]

In our institution, it was not until 2017, that sugammadex was available in the department of anesthesia as an alternative to neostigmine and atropine. Because of its high cost and lack of experience in clinical practice, it had not become a routine reversal agent for rocuronium-induced deep neuromuscular blockade. Therefore, we conducted this study to investigate the efficacy of sugammadex on deep neuromuscular blockade reversal in patients undergoing laparoscopic colorectal resection.

2. METHODOLOGY

2.1. Study design

A prospective, observational study was conducted between September 2018 and May 2019, in adults aged 18 y and over, undergoing laparoscopic colorectal resection surgery under general anesthesia at the Department of Anesthesia of the University Medical Center Ho Chi Minh City, with rocuronium-induced deep neuromuscular blockade. The study was conducted according to the STROBE guidelines for observational studies. It is a 1000-bed teaching hospital, with approximately 400 scheduled operations performed each week, with a standard length of stay in the PACU of 4 to 6 hours for each patient.

2.2. Patient selection

Patients aged 18 y of age or above and ASA Class I, II, or III were enrolled. The exclusion criteria were: (i) known or suspected hypersensitivity to sugammadex or any of the medication used during general anesthesia; (ii) family history of malignant hyperthermia; (iii) severe renal impairment (CrCl < 30 ml/min) or severe hepatic impairment or chronic heart failure (NYHA class III or IV); (iv) hypokalemia, hypo- or hyper-calcemia, muscular dysfunction or currently using medications that might affect the neuromuscular system (including but not limited to magnesium, antiepileptics, aminoglycoside antibiotic); (v) suspected difficult intubation; (vi) risk of massive bleeding or conversion to open surgery; (vii) obesity (BMI ≥ 30 kg/m^2); and (viii) pregnancy or breast-feeding.

All patients were admitted for elective laparoscopic colorectal resection surgery during the study period, found eligible for the study, were included.

2.3. Procedure

In the preoperative period, all eligible patients were evaluated by an anesthesiologist within 24 h before surgery according to the hospital standard protocol. The clinician also explained the purpose of the study and obtained the consent papers from the patients or patients' caregivers.

In the operating room, routine monitoring included electrocardiography, pulse oximeter, non-invasive blood pressure, capnography, and central temperature monitoring. Acceleromyography (TOF-Watch ® SX – Organon Ireland Ltd.) was applied to the opposite hand with the blood pressure cuff. Its electrodes were placed on the ulnar nerve, the Hand Adapter was attached to the thumb, and the acceleration transducer was attached to the distal portion of the Hand Adapter.

Calibration and stabilization of the TOF-Watch were performed after the injection of propofol and before injecting rocuronium. Induction of anesthesia was achieved with fentanyl 1.5–3 µg/kg, propofol 1.5–2.5 mg/kg, and rocuronium 0.6 mg/kg intravenously. Endotracheal intubation was performed after confirming TOF = 0

General anesthesia was maintained with sevoflurane targeting 1.5–3 minimum alveolar concentration (MAC), rocuronium 0.15 mg/kg when post-tetanic count (PTC) > 2. Deep level of neuromuscular blockade was maintained during surgery, targeting TOF = 0 and PTC = 1–2. Rocuronium 0.15 mg/kg was administered when PTC > 2.

At the end of the surgery the time of administration of the last rocuronium was recorded. Sugammadex dosage was decided by the TOF value at the end of the surgery: 4 mg/kg if TOF = 0 and 2 mg/kg if TOF = 1–2. Sugammadex (Bridion®– Merck Sharp & Dohme, The Netherlands) 100 mg/ml was administered by slow intravenous injection within 10 seconds.

Fentanyl infusion was discontinued, sevoflurane was continued at a minimum volume and the TOF ratio was monitored every 15 sec until TOF ratio ≥ 0.9 was achieved. The patients were extubated when the anesthesiologists decided it was appropriate and then transferred to the PACU.

In the PACU, TOF ratio was continued to be monitored 15 min after the patients' arrival at the PACU and then every 30 min for 2 h, or whenever the patient showed any signs of respiratory distress. The patients were monitored in the PACU according to the hospital

Table 1: Demographics and baseline characteristics of 59 participants

Characteristics	Frequency (n = 59)
Gender	
Male	32 (54.2)
Age (y)	60.3 ± 13.7
Weight (kg)	55.5 ± 9.2
Height (cm)	159.6 ± 8.8
BMI (kg/cm^2)	
≥ 25	10 (16.9)
18.5 – < 25	40 (67.8)
< 18.5	9 (15.3)
Mean	21.8 ± 3.2
ASA Class	
I	6 (10.2)
II	44 (74.6)
III	9 (15.3)
Comorbidities	
Hypertension	20 (33.9)
Diabetes mellitus	10 (16.9)
Chronic ischemic heart disease	5 (8.5)
Asthma	2 (3.4)
Valvular heart disease	1 (1.7)
Values are given as frequency (percentage) or mean ± SD	

standard Enhanced Recovery After Surgery (ERAS) protocol for colorectal surgery.

2.4. Data collection and study outcomes

Patients' characteristics, including demographics, ASA physical status, comorbidities, clinical history, and laboratory tests were collected during the admission at the hospital and extracted from the electronic medical records. During the surgery, we collected data on operative duration, anesthesia duration, time from the last dose of rocuronium to the time of administration of sugammadex, and total dose of rocuronium and fentanyl used. Operative duration was defined as the time from incision to closing the wound. Anesthesia duration was defined as the time from the induction of anesthesia to the time of withdrawal of all of the anesthetic agents.

The primary outcome was the time between the administration of sugammadex to the recovery of TOF ratio ≥ 0.9. Secondary outcomes included (i) incidence of deep neuromuscular blockade at the time of sugammadex administration, and (ii) incidence of residual neuromuscular blockade. Residual neuromuscular blockade was defined as TOF ratio < 0.9 in 3 consecutive measurements at any time point in the PACU or any clinical evidence of residual neuromuscular blockade based on observations during routine care; e.g., blood gas analysis, oxygen saturation, respiratory rate.[9]

2.5. Statistical analyses

The t-test or Mann-Whitney test was applied to compare the baseline characteristics between the two groups for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. All analyses were performed using SPSS version 20.0 with a significance level of 5%.

3. RESULTS

3.1. Clinical & demographic parameters

From October 01, 2018 to April 28, 2019, 59 patients undergoing elective laparoscopic colorectal resection were included in the study. Approximately half of the patients were 60 y or above, with a mean age of 60.3. There was a balance between the proportion of males and females in the study, 32 and 37 patients, respectively. The most common recorded comorbidities were hypertension 33.9% and diabetes mellitus 16.9%. Only a small proportion of the participants had respiratory and cardiovascular disorders; 3.4% and 8.5% respectively. Almost three-quarters of the participants were classified as class II ASA (74.6%). The average duration of surgery and duration of anesthesia was 164.5 min and 197.9 min,

Table 2: Surgical and anesthetic characteristics (all-subjects-treated population, n = 59)

Variables	Values (n = 59)
Duration of surgery (min)	164.5 ± 52.0
Duration of anesthesia (min)	197.9 ± 53.9
The time between the last administration of rocuronium and the administration of sugammadex (min)	42.1 ± 13.3
Total dose of rocuronium (mg)	83.9 ± 21.2
Total dose of fentanyl (mcg)	219.0 ± 54.3
Patient's temperature at the end of the surgery (°C)	36.2 ± 0.6
Values are given as mean ± SD	

Table 3: Time from administration of sugammadex to recovery of TOF ratio of 0.9, TOF ratio before administrating sugammadex, TOF ratio in the PACU, and the incidence of residual neuromuscular blockage (n = 59)

Variables	Values
Primary outcome	
Time to achieve TOF ratio ≥ 0.9 (min)	4.0 ± 1.8
Maximum	8.9
Minimum	1.5
4 mg/kg group	4.2 ± 1.8
2 mg/kg group	3.7 ± 1.8
Secondary outcomes	
TOF ratio at the end of the surgery (before injecting sugammadex)	
TOF ratio = 0	37 (62.7%)
TOF ratio > 0	22 (37.3%)
TOF ratio at various time points in the PACU (%)	
At admission	96.6 ± 2.9
At 15 min	97.7 ± 2.2
At 30 min	98.8 ± 1.6
At 60 min	99.0 ± 1.4
At 90 min	99.7 ± 0.7
At 120 min	99.9 ± 0.3
Incidence of residual neuromuscular blockade	0 (0%)

Values are given as frequency (percentage) or mean ± SD

respectively. All patients received rocuronium for deep neuromuscular blockade with an average dose of 83.9 mg. Details about the demographic and surgical characteristics of the study population are described in Table 1 and Table 2.

3.2. Outcomes

The average time to achieve a TOF ratio of ≥ 0.9 was 4.0 min (ranging from 1.5 min to 8.9 min). At the end of the surgery, most of the patients were still under the deep level of neuromuscular blockade with the TOF ratio of 0, 62.7% of the study population, and received a 4 mg/kg dose of sugammadex. It took an average of 4.2 min to reach a TOF ratio of ≥ 0.9 in this group. The remaining patients received a 2 mg/kg dose of sugammadex, with an average time to fully recover neuromuscular function of 3.7 min. All of the TOF ratio values recorded at various time points in the PACU were above 96%. No pulmonary complication in the PACU was recorded. Table 3 shows the information on the primary and secondary endpoints of the study.

3.3. Factors of prolonged recovery

Among patients' demographic and clinical characteristics, univariate analyses identified that older age and higher ASA class were associated with prolonged time to recovery using sugammadex (Table 4).

4. DISCUSSION

We conducted a study investigating the efficacy and safety use of sugammadex in a complete reversal of neuromuscular blockade in patients undergoing elective laparoscopic colorectal resection in a tertiary teaching hospital. Results from our study showed that sugammadex produced a rapid recovery from both moderate or deep neuromuscular blockade induced by rocuronium. At the end of the surgery, most patients were still under a deep level of blockade and there was no incidence of residual paralysis.

4.1. Time to fully recover from deep neuromuscular blockade

Results from our study were consistent with those reported in the literature, indicating that it took a rapid time to achieve a TOF ratio of 0.9 following the administration of sugammadex regardless of the depth of neuromuscular blockade. However, the geometric recovery time recorded in our study for both regimens was approximately 1 – 1.5 min longer than those reported in previous studies.[6,10,11] The rationale for the sugammadex dose in our study was the standard dosage from the product label information as well as the findings from a previous dose-finding, phase II study of sugammadex, which showed that reversal of neuromuscular blockade was obtained with sugammadex after 3.3 and 1.9 min in the 4 mg/kg and 2 mg/kg groups, respectively.[12] A recent systematic review and meta-analysis conducted by Hristovska and colleagues reported that the time to reversal of neuromuscular blockade from second twitch and from the post-tetanic count of 1-5 to a TOF ratio of 0.9 was 2 min and 2.9 min, respectively.[13] Although reversal of the TOF ratio to 0.9 occurred within 5 min in most patients using sugammadex, there had been reports of outliers and a wide inter-individual variation in the speed of reversal of sugammadex. For example, the time to fully recover neuromuscular function could be rapidly

Table 4: Factors that were associated with time to fully recover neuromuscular function

Variables		Frequency (%) (n = 59)	Time to reach TOF ratio ≥ 0.9	P-value
Sugammadex dose (mg/kg)	4	37 (62.7)	4.2 ± 1.8	0.255
	2	22 (37.4)	3.7 ± 1.8	
BMI (kg/cm^2)	< 18.5	9 (15.3)	4.8 ± 1.9	0.491
	18.5 – 22.99	29 (49.2)	4.0 ± 1.9	
	23 – 24.99	11 (18.6)	3.7 ± 2.1	
	≥ 25	10 (16.9)	3.6 ± 1.4	
ASA classification	I	6 (10.2)	3.0 ± 1.2	**0.042**
	II	44 (74.6)	3.9 ± 1.6	
	III	9 (15.3)	5.3 ± 2.8	
Age (y)	< 65	36 (61)	3.4 ± 1.3	**< 0.001**
	≥ 65	23 (39)	4.9 ± 2.2	
Gender	Male	32 (54.2)	4.25 ± 2.2	0.291
	Female	27 (45.8)	3.74 ± 1.3	
Time between the last administration of rocuronium and the administration of sugammadex (min)	< 42	37 (62.7)	4.0 ±1.6	0.743
	≥ 42	22 (37.3)	4.1 ± 2.3	
Duration of anesthesia (min)	< 120	6 (10.2)	5.0 ± 2.2	0.327
	120 – 180	15 (25.4)	3.7 ± 1.6	
	>180	38 (64.4)	4.0 ± 1.8	
Total rocuronium used (mg)	< 83	33 (55.9)	4.1 ± 1.6	0.832
	≥ 83	26 (44.1)	4.0 ± 2.1	
Total fentanyl used (µg)	< 218	40 (67.8)	3.9 ± 1.7	0.397
	≥ 218	19 (32.2)	4.3 ± 2.0	

Values are given as frequency (percentage) or mean ± SD

achieved at 0.8 min or could be prolonged to 24.6 min in patients under deep neuromuscular blockade.[14,15] Another reason for the discrepancy might be from the difference in ethics among studies. Previous studies had shown that both geometric time to recovery of TOF 0.9 following sugammadex or neostigmine and spontaneous recovery from rocuronium were lower in Chinese in comparison to Caucasian subjects, due to differences in pharmacokinetic and pharmacodynamic related factors such as differences in lipid store, volume of distribution and decreased α-1-acid glycoprotein.[16,17]

At the time of administration of sugammadex, 62.7% of patients were still under the deep level of neuromuscular blockade with a TOF ratio of 0. This is a very important finding because previous data suggested that at this point, most of the patients would have been able to partially recover their neuromuscular function. Published pharmacokinetic parameters and simulation of the rocuronium pattern of recovery showed that patients could return to the moderate to shallow level of blockade after only 25 min following rocuronium.[18] Meanwhile, the present study showed that even at 42 min, most of the patients did not have the first twitch recorded by the TOF Watch. If the physicians relied solely on the literature and clinical assessment, a lot of patients would be put at the risk of choosing the wrong reversal agents (since neostigmine only worked after TOF count reached a value above 1) or sugammadex underdosing (2 mg/kg instead of 4 mg/kg for deep blockade). This finding highlighted the importance of monitoring neuromuscular

function during anesthesia so that the physicians could precisely evaluate the level of blockade at the end of surgery to determine which reversal drugs and at which dosage was appropriate.

Deep neuromuscular blockade, has been proven to provide better surgical conditions by reducing muscle tension in the abdominal wall and preventing intraoperative spontaneous muscle movements. However, the beneficial effects of the deep blockade on other outcomes such as duration of surgery, complications, blood loss, length of stay, and quality of recovery were still not cleared.[5,19] It is often a routine practice to administer a bolus dose of neuromuscular blockade agent whenever a surgeon feels resistance in the abdomen, however, this practice is mostly based on the surgeons' subjective assessment during the surgeries and therefore might lead to the use of unnecessary doses of neuromuscular blocking agents. Our study showed that there was no incidence of residual paralysis in the PACU, which was a better result than expected since previous trials had reported a higher incidence of residual paralysis following the administration of sugammadex.[3,20] Kotake and colleagues reported an incidence of 4.3% of the participants who had a TOF ratio < 0.9 after extubation, which led to the conclusion that the use of sugammadex could not eliminate the risk of residual paralysis. However, neuromuscular monitoring (both objective and subjective) was not applied in the clinical setting of this study and could diminish the beneficial effect of sugammadex. In fact, with proper quantitative and qualitative monitoring, a later study conducted by Brueckmann showed that a residual paralysis of 0% following sugammadex was not unachievable.[21]

4.2. Factors associated with prolonged recovery

In concordance with previous studies, we found that old age was a factor associated with prolonged time to recovery following sugammadex.[22,23] This phenomenon could be explained by physiologic and pharmacokinetics changes of the advancing age. The lower cardiac output and poor peripheral perfusion in the elderly would result in a slow increase in plasma concentration of sugammadex and a slower decrease in rocuronium concentration in comparison to their younger peers. A decrease in renal function is also a factor that could reduce the clearance of the sugammadex-rocuronium complex since this complex is mostly eliminated by the kidneys.[24]

In our study, there was approximately a 1.5-min delay in the time to recover of neuromuscular function in the above 65-year-old group (4.9 min versus 3.4 min), which was not clinically significant, as long as neuromuscular monitoring was maintained. In addition, many studies suggested that the delay in time to recovery was not associated with reduced efficacy of the drug or increased incidence of adverse outcomes among older patients.[24] Our study also found that high surgical risk ASA was also associated with the delay in the effect of sugammadex. There was a lack of evidence in the literature to support our findings. However, patients with a high class of ASA usually had complex underlying comorbidities; therefore the physicians need to be more careful in interpreting values recorded by the TOF watch, before declaring whether the patients were fully recovered or not. Moreover, studies on sugammadex among this high-risk population usually focused on safety outcomes, in particular, cardiovascular adverse events.[25] Therefore, this finding served as a notice for physicians to be more cautious when deciding the appropriate time to extubate these patients.

5. LIMITATIONS

There are several limitations of this study that must be noted. Firstly, we did not report the incidence of adverse outcomes such as pulmonary complications after extubating nor compare its efficacy and safety to the current standard reversal agents neostigmine and atropine. Although sugammadex had been proven to be able to rapidly reverse the effect of rocuronium and vecuronium, the high cost prevented it from being a standard reversal agent of choice in clinical practice, especially in middle-income countries like Vietnam. Therefore, whether or not the use of sugammadex was cost-effective needed to be assessed thoroughly based on multiple factors regarding postoperative complications or operating turnover time. These could be a topic worth exploring for future research. Secondly, the small sample size and the single-center nature of this study made it difficult to detect the actual prevalence of residual neuromuscular following sugammadex in the general public.

6. STRENGTHS

One of the strengths of our study was that this was one of the first studies in Vietnam that demonstrated the efficacy and safety with the use of sugammadex in a complete reversal of neuromuscular blockade in patients undergoing elective laparoscopic colorectal resection. Thanks to the prospective nature of the study, the results could represent the practice of neuromuscular blockade reversal in such a setting of middle-income countries. In addition, our hospital was one of the first hospitals in Vietnam to use sugammadex as a reversal agent, especially in high-risk patients such as obesity, patients with underlying cardiovascular and respiratory comorbidities, and patients with neuromuscular

disorders. At the time our study was conducted, the cost of sugammadex had not been covered by the national insurance, because of its high cost and there was a lack of experience of its use as well as evidence regarding its efficacy and safety. Results from this study are the first step to support the implementation of a routine practice including neuromuscular monitoring and using sugammadex as a reversal agent for rocuronium-induced neuromuscular blockade during surgery, which was concordance with the latest recommendations from the American Society of Anesthesiologists Practice Guidelines.[26]

7. CONCLUSIONS

Sugammadex was effective and safe for the reversal of deep neuromuscular blockade in laparoscopic colorectal resection and should be used routinely in combination with continuous neuromuscular monitoring as a part of the ERAS program.

8. Data availability

The numerical data generated during this research is available with the authors.

9. Conflict of interest

The authors declare that there are no conflicts of interest

10. Ethical issues

The participants and their caregivers (if any) were provided with written and verbal information about the purpose and content of the study. After agreeing to participate in the study, they were asked to sign a registration form for confirmation. All the information regarding the research subjects was confidential

The study was approved by the Ethics Council of the University of Medicine and Pharmacy at Ho Chi Minh City (Approval reference number: 310/ĐHYD-HĐĐĐ; Date of approval: September 14, 2018). The procedures used in this study adhered to the tenets of the Declaration of Helsinki.

11. Authors' contribution

VTNP: conceptualization, methodology, writing the original draft, review and editing the manuscript, supervision

DTN: literature search, formal analysis, interpretation of data, writing original draft

HTP: literature search, acquisition of data, writing original draft

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