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ARTICLE

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ABSTRACT

Introduction: Titration of neuromuscular block (NMB) plays a key role in intraoperative recurrent laryngeal nerve monitoring during thyroid surgery. The combination of neuromuscular blocking agent and timely partial reversal of NMB was investigated in both animal experiments and clinical neuro-monitored thyroidectomy.
Methods: In animal experiments, 8 piglets received sugammadex to assess the laryngeal EMG recovery after rocuronium-induced NMB. In clinical monitored thyroidectomy, 40 patients each were allocated to conventional group and sugammadex group. Conventional group received rocuronium 0.3 mg/kg at anesthesia induction, while sugammadex group received partial NMB recovery protocol- 0.6 mg/kg of rocuronium at anesthesia induction and 0.5 mg/kg of sugammadex. Main outcome was assessed by first (V1) and final (V2) EMG signal induced by vagal stimulation.
Results: In the porcine model, 50% recovery of laryngeal EMG amplitude was achieved at 16.8 ± 1.9 and 6 ± 2.7 minutes respectively after 0.5 and 1 mg/kg of sugammadex ($p < 0.01$). In monitored thyroidectomy, EMG amplitudes at V1 in group S and group C were 1214 ± 623 and 915 ± 476 μV, respectively ($p = 0.02$). Positive and adequately high EMG amplitudes were observed at the early surgical stage for all patients. Sugammadex groups were superior to conventional group in EMG tube placement ($p < 0.001$).
Conclusion: Both porcine model and clinical application showed that precise NMB management by low-dose sugammadex was effective for intraoperative neural monitoring (IONM). The regimen ensured optimal conditions for tracheal intubation and timely neuromuscular function restoration for high-quality EMG signal.

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Thyroid surgery; intraoperative neural monitoring (IONM); recurrent laryngeal nerve (RLN); neuromuscular blocking agent (NMBA); sugammadex; anesthesia

Introduction

Nerve injury to recurrent laryngeal nerve (RLN) and/or external branches of superior laryngeal nerve (EBSLN) are one of serious complications related to the thyroid and parathyroid surgery. In recent decades, thyroid surgeons are devoted to reduce these complications by intraoperative neural monitoring (IONM) system. IONM could be used to map and identify the RLN and EBSLN, to detect nerve anatomic variations, to elucidate injury mechanisms and to predicting the prognosis of invaded or injured RLN to modify the surgical plans.[1–11]

Neuromuscular blocking agents (NMBA) are generally accepted as routine anesthesia practice for tracheal intubation and neck surgery. The proper administration of an NMBA is a key element of anesthesia to ensure successful IONM.[12–16] To minimize the effect of NMBA on reduction of EMG signal and subsequent interpretation, sugammadex could be used to timely and effectively reverse rocuronium-induced neuromuscular block (NMB). Sugammadex as an antagonist to steroidal NMBA is applied in patients requiring IONM during thyroid or parotid surgery.[17–19]

There is a controversy between routine and selective reversal of NMB with sugammadex in monitored thyroidectomy. In our previous study, we confirmed a routine fully-NMB-reversal protocol with sugammadex (2 mg/kg) provided both excellent intubation condition and high initial EMG signal of IONM in 100% of 50 patients.[17] In contrast, Empis et al. reported a selective sugammadex-reversal protocol and showed that sugammadex is required only 15 (12.5%) of 120 patients to enhance the first (V1) EMG signal induced by vagal stimulation (V_1).[18] However, the selective protocol may result in a false-negative interpretation and

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Table 1. Protocol of precision neuromuscular blockade managemengt by low-dose sugammadex for intraoperative neural monitoring during thyroid surgery (clinical application).

Perioperative stage	Remarks
Preoperative evaluation	ASA physical status with upper airway assessment
Monitoring setup	Standard NMT monitoring
Anesthesia induction	Full dose of steroidal neuromuscular blocking agent (NMBA)
Induction	Fentanyl 1mcg/kg, lidocaine 1mg/kg and propofol 2 mg/kg
NMBA	Rocuronium 0.6 mg/kg
Anesthesia maintenance	
Inhaled anesthetic	Sevoflurane 2-4%
Intravenous anesthetics	Propofol TCI, concentration: 1–2 mcg/kg
Anesthesia depth	BIS or Entropy at 40–60 if available
Vasopressor	Ephedrine 8–12 mg if hypotension occurred
Neural monitoring	Partial reversal of neuromuscular blockade
Operation	Sugammadex 0.5 mg/kg at 10 min after skin incision
V1 and V2 signal	EMG amplitude correlated with TOF ratio
Anesthesia emergency	
Extubation	Sugammadex 1.5 mg/kg
	Extubation when TOF ratio reach 1.0
Pain control	Fentanyl 1mcg/kg with NSAID if not contraindicated
Postoperative evaluation	Anesthesia adverse events and satisfaction

NMT = neuromuscular transmission, TCI = target-controlled infusion, BIS = Bispectral index, V1 and V2 = initial and final vagal stimulation, TOF ratio = train-of-four mode in NMT monitor.
Conventional protocol was identical to low-dose sugammadex protocol except for the dose of rocuronium and absence of sugammadex.

the initial EMG response may have wide individual difference.[20,21]

Since muscle relaxation is also required during surgery, complete neuromuscular function recovery with sugammadex (2 mg/kg) might not be the best management protocol. Complete neuromuscular function recovery is associated with body movement during surgery; hence, more anesthetics and analgesics are required. Therefore, the use of lower dosage of sugammadex (1.0 or 0.5 mg/kg) to induce a partial neuromuscular function recovery could be a better alternative anesthesia strategy for monitored thyroidectomy. Few reports discuss administration of sugammadex during surgery for neural monitoring purposes, and data are still lacking on partial reversal of NMB by low-dose sugammadex for monitored thyroidectomy.

The study was aimed to assess the best timing of precise sugammadex dose to meet the needs of both monitored thyroidectomy and anesthesia through both porcine model and clinical practice during monitored thyroidectomies. According to international guidelines and update IONM outcomes, there are two departmental protocols in practice 1) conventional protocol: rocuronium 0.3 mg/kg at induction with spontaneous recovery and 2) update protocol: rocuronium 0.6 mg/kg at induction with sugammadex 2 mg/kg at skin incision. Porcine model was designed to improve second protocol by determining the feasibility of low dose sugammadex. Our hypothesis was that a partial reversal of NMB by low dose (0.5 or 1 mg/kg) sugammadex would also allow a timely neural monitoring signals

Materials and methods

Porcine model

Eight Kaohsiung Animal Propagation Station black pigs (KHAPS black pigs) weighted 18 to 22 kg were fasted (but given water) for 8 hours before the operations. The Institutional Animal Care and Use Committee of XXXX University approved our porcine model (protocol No: 107036). All animal experiments in piglets were followed institutional guidelines which assure compliance to international regulations and national policy. We used a well-established porcine model[22,23] to evoke and record EMG signal from vocalis muscle via the EMG tube or needle electrodes.The parameters of EMG signals are highly similar to human profile such as threshold, latency and amplitude.[24–26]

Anesthesia was initiated by administrating 2 mg/kg of tiletamine/zolazepam intramuscularly 30 min before the experiment. General anesthesia induction was performed by inhaled sevoflurane (2-4%) with oxygen 2～3 L/min via a designed plastic mask in the supine position. An EMG endotracheal tube with 6 mm inner diameter (Medtronic, Jacksonville, FL) was placed for each animal. Maintenance of general anesthesia was kept by sevoflurane 1-3% with control ventilation. Physical status of the animals was observed by the Vista 120 physiological monitor (Draeger, Lübeck, Germany) until the end of the experiment.

The continuous IONM (C-IONM) model to measure real-time EMG signal changed by NMB management was setup as previously described.[17] An automated periodic stimulation (APS) was applied to the vagus nerve. CIONM was carried out using the following commercially available equipment: 2 mm APS Electrode Stimulator probe, NIM Standard Reinforced EMG endotracheal tube, and NIM 3.0 Nerve Monitoring System (Medtronic, Jacksonville, FL) with a pulse generator for continuous stimulation (1/second, 100 μs, 3 mA), and an EMG amplifier.[17]

A total of 8 piglets were allocated into two groups with 4 piglets in each group. A complete NMB was induced by an intravenous bolus of rocuronium 0.6 mg/kg in each piglet. A three-minute interval observation was done before sugammadex. Intravenously sugammadex (0.5 or 1.0 mg/kg) was randomly injected to reverse NMB . Time course of continuously laryngeal EMG signals was recorded for 30 minutes in each piglet. Recovery time of EMG amplitude

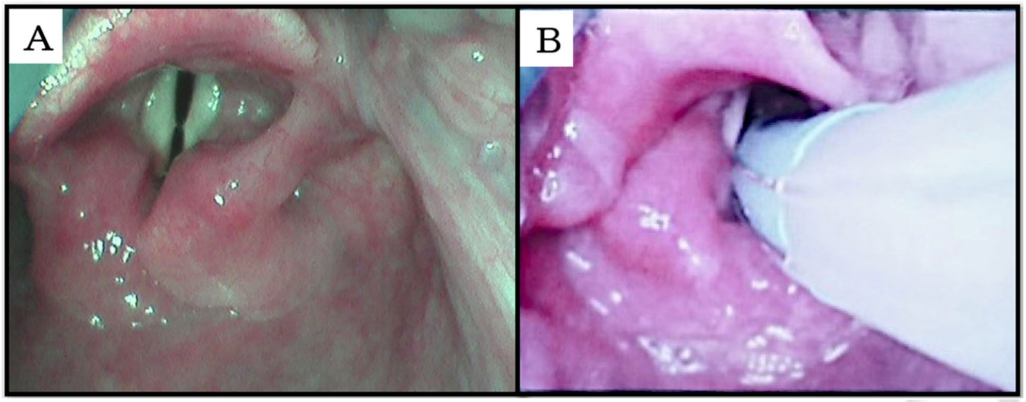

Figure 1. The steps of the EMG tube placement and surface electrode confirmation by the UEScope (clinical application). 1 A) Typical full visualization of the glottis in a patient. 1B) Two pairs of surface electrodes are advanced perpendicular to the vocal cords until they reach the proper depth.

was measured at 3 time points: 1) detectable signal, 2) 50% of baseline, and 3) 80% of baseline value.

Clinical application

We reviewed medical records of 80 patients (61 women; age from 24 to 80 years old) undergoing total thyroidectomy or total lobectomy under routine IONM assistance from Jan 2017 to Dec 2018. The Institutional Review Board of XXXX University Hospital approved this clinical trial (KMUH-IRB-E(I)-20190164). All 80 patients were cared by single surgeon and experienced anesthesiologists. The IONM equipment setup, procedures and loss of signal algorithm followed the International Neural Monitoring Study Group Guidelines.[1–4]

General anesthesia induction was done by lidocaine (2 mg/kg), fentanyl (1 μg/kg) and propofol (2 mg/kg) for each patient. Patients were segregated into control group (Group C, $n = 40$) if they received conventional anesthesia protocol with rocuronium of one effective dose (0.3 mg/kg) for anesthesia induction. In the sugammadex group (Group S, $n = 40$), patients had received precision anesthesia protocol with rocuronium of standard dose (0.6 mg/kg) for anesthesia induction and low sugammadex dose (0.5 mg/kg) was administered intravenously 10 minutes after skin incision, (Table 1). All patients were subjected to a standard neural monitoring anesthesia protocol for thyroidectomy except NMBA regimen.

A reinforced EMG endotracheal tube (internal diameter (ID) 6.0 mm for female and 7.0 mm for male patients, respectively) (Medtronic, Jacksonville, FL) was placed by the UEScope (UE Medical Devices, Newton, MA). The EMG tube was then advanced under video guidance until the surface electrodes were in optimal contact with vocal cords (Figure 1). Proper tube depth and invisible tube rotation were then visually verified by video image and anesthesia was maintained with sevoflurane combined with propofol target-controlled infusion. The precision anesthesia protocol (Group S) included anesthesia depth and NMB management: At 10 minutes after operation starting, an intravenous bolus of sugammadex 0.5 mg/kg was administrated to partially reverse NMB (Figure 2). No additional rocuronium was given intraoperatively to any patient. Train-of-four

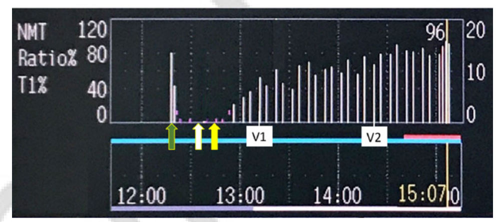

Figure 2. Typical time sequence of intraoperative neuromuscular transmission (NMT) monitoring in a patient with precision anesthesia protocol (clinical application). Green arrow: At anesthesia induction, the NMT was intact and baseline TOF ratio was around 100%. White arrow: At skin incision, complete neuromuscular blockade was noted. The TOF response showed none of NMT and first twitch (T1) were 0%. Yellow arrow: At 10 minutes after skin incision, sugammadex was given and NMT recovered gradually. V1= first vagal stimulation. V2= final vagal stimulation.

(TOF) ratio derived via neuromuscular transmission (NMT) monitor (Aestiva/5; Datex-Ohmeda, FL) was used to continuously assess NMB degree of the adductor pollicis muscle. The train of four (TOF) stimulation was setup as (constant 50 mA current, four twitches at every 0.5 second over 2 seconds). Anesthesia depth was monitored by Bispectral index (BIS) monitor (Medtronic, MN). Target anesthesia depth was controlled via titration by inhaled sevoflurane to keep Bispectral index (BIS) monitor between 40% and 50%.

All thyroid surgery followed standard IONM procedures,[27,28] and the highest EMG amplitudes were captured, registered, and compared. V_1 and V_2 signal was defined as first vagal stimulation before thyroid dissection and final vagal stimulation after thyroid resection, respectively.

Main outcome was assessed by V_1 and V_2 amplitude (μV) between groups; time course of hemodynamic parameters and degree of NMB were also compared; while other outcomes included physical characteristics, adverse events and postoperative surgical outcomes. Extubation time was defined as time interval from skin closure to EMG tube removal. Each patient received laryngofiberoscopic examination to obtain vocal cord mobility recordings at the day before and after surgery. When abnormal vocal cord movement was noticed after operation, the recording before operation was used to compare.

To ensure adequate power for the study, the minimal sample size was 20 patients in each group according to previous study.[29] We reviewed records of 40 patients to show

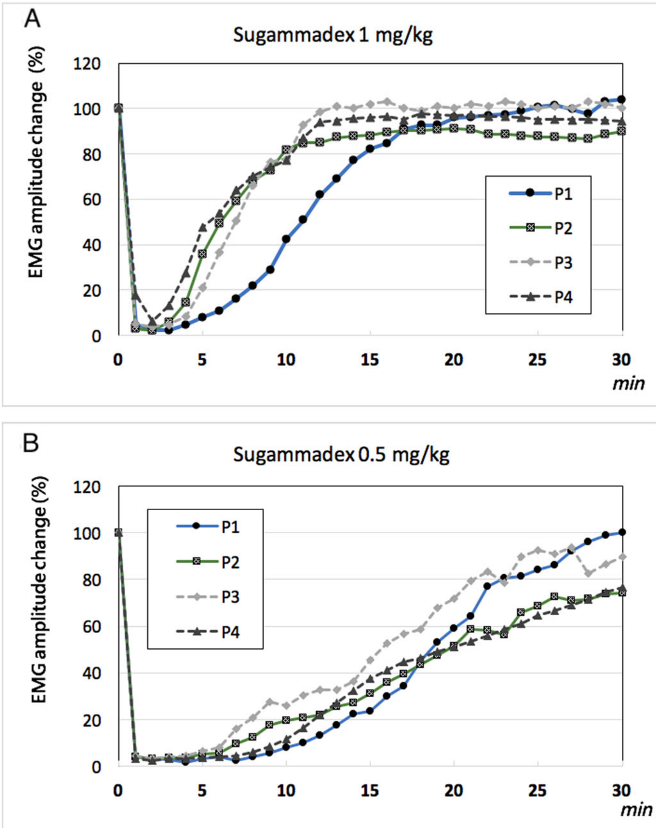

Figure 3. Tracing of laryngeal EMG amplitude of partial neuromuscular blockade reversal in each piglet (porcine model). Piglets received an intravenous bolus of rocuronium 0.6 mg/kg to induce complete neuromuscular block. Two minutes later, a bolus of sugammadex 1 mg/kg (3 A) or 0.5 mg/kg (3B) was randomly injected. The observation period for laryngeal EMG recovery was 30 minutes.

at least 20% difference in EMG amplitude with a power of 0.9 and a type 1 error of 0.05. All data are presented as mean (standard deviation). Statistical analysis of continuous variables between two groups was carried out by the 2-sample *t*-test. Categorical variables were carried out by the chi-square test or the Fisher exact test. All statistical analysis was 2-tailed, and a $p < 0$ .05 was of statistical significance.

Results

In porcine model, rocuronium 0.6 mg/kg suppressed the EMG signal in all 8 piglets within a minute. Figure 3 shows tracing of laryngeal EMG amplitude of partial NMB reversal by low-dose sugammadex in individual piglets. It took 2.3 ± 1.0 and 6.5 ± 2.3 minutes to obtain detectable EMG signals (amplitude $>100_{\mu}$V) after sugammadex 1.0 and 0.5 mg/kg respectively ($p = 0.005$). Sugammadex 1 mg/kg showed significantly faster EMG recovery to 50% (6.0 ± 2.7 vs. 16.8 ± 1.9 min) and 80% (9.8 ± 2.2 vs. 24.3 ± 3.3 min) baseline value than did sugammadex 0.5 mg/kg (both $p < 0.01$). In this porcine model, no significant changes in arterial blood pressure, heart rate and EKG rhythm were noted during vagal nerve stimulation and sugammadex administration. There was also no sign of residual blockade with observation at 30 minutes.

In the clinical trial, detailed characteristics of 80 patients are shown in Table 2. There were 137 nerves at risks, and we encountered one temporary and one permanent RLN palsy in two thyroid cancer patients. Most patients experienced excellent and good intubation quality and all EMG tubes placement were successful at the first attempt. Patients in group S (rocuronium 0.6 mg/kg during induction, and sugammadex 0.5 mg/kg 10 minutes after skin incision) had better intubation condition than those in group C (rocuronium 0.3 mg/kg during induction only) ($p = 0.002$).

Time interval from anesthesia induction (rocuronium injection) to V_1 and V_2 stimulation did not differ significantly between groups as shown in Table 3. It took an average of 18.5 ± 10.2 minutes from sugammadex injection to V_1 stimulation in group S. Figure 2 demonstrates typical time sequence of intraoperative neuromuscular transmission in a patient with partial reversal of NMB. Time course of precision anesthesia protocol including neuromuscular transmission and anesthesia depth during monitored thyroidectomy is depicted in Figure 4.

Neuromuscular blockage degree and EMG amplitude were compared at V_1 and V_2 stimulations between the two groups. At V_1 stimulation, patients in group S showed higher EMG amplitude ($1214 \pm 623\,\mu$V vs. $915 \pm 476\,\mu$V, $p = 0.02$) and Train-of-four (TOF) ratio (58.7 ± 17.1 vs. 44.9 ± 20.1, $p = 0.002$) than group C patients (Table 3). Patients in group S showed comparable EMG amplitude and TOF ratio as group C patients at V2 stimulation (both $p > 0.05$). Extubation time did not differ significantly between the two groups (Table 3). None of the patients had clinical event due to recurrent or residual NMB after sugammadex injection.

Discussion

In this porcine model, 0.6 mg/kg of rocuronium dose was used to induce a complete NMB. Both 1 mg/kg and 0.5 mg/kg sugammadex doses showed at least approximate 80% laryngeal EMG amplitude recovery within a 30-minute observation period. It took an average of 6 and 17 minutes to achieve 50% EMG amplitude recovery by sugammadex 1 and 0.5 mg/kg, respectively. Similarly, the clinical application shows the precision neuromuscular management protocol with low-dose sugammadex (0.5 mg/kg) provided timely and high-quality laryngeal EMG signal (mean amplitude $1214\,\mu$V after average of 18.5 minutes from sugammadex injection). It facilitated better intubation condition, faster neuromuscular recovery and higher EMG signals compared to conventional anesthesia protocol (single one effective rocuronium dose at anesthesia induction). To the best of our knowledge, this is the first study using low-dose sugammadex (0.5 mg/kg) to obtain partially reversal of NMB during IONM in thyroid surgery.

Many anesthesia protocols have been developed to minimize the interference of anesthesia on the IONM system during thyroid surgery. The degree of NMB is one of the major anesthesia factors that has been investigated over decades. If NMB degree is not titrated for IONM, EMG

Table 2. Patient characteristics of 80 patients receiving monitored thyroidectomy with conventional and low-dose sugammadex protocols (clinical application).

	Sugammadex (S Group, $n = 40$)	Conventional (C Group, $n = 40$)	P value
Female: Male (n)	30:10	31:9	0.79
Age (yr)	50.0 ± 11.5	50.6 ± 13.9	0.82
Weight (kg)	64.9 ± 13.4	62.9 ± 14.7	0.51
Height (cm)	161.4 ± 8.0	161.1 ± 7.5	0.86
BMI (kg/m^2)	**24.8 ± 3.9**	**24.0 ± 4.1**	**0.36**
Intubation condition			<0.001
Excellent/good/poor	23/17/0	12/26/2	
Vasopressor* (n)	2 (5%)	5 (12.5%)	0.23
Benign/Cancer	26/14	30/10	0.32
Nerve at risk (n)	72	65	
Temporary palsy (n)	0(0%)	1(1.5%)	0.34
Permanent palsy (n)	0(0%)	1(1.5%)	0.34
Post-op hematoma (n)	0(0%)	0(0%)	1.0

BMI = body mass index.
S group (rocuronium 0.6 mg/kg during induction, and sugammadex 0.5 mg/kg 10 minutes after skin incision), C group (rocuronium 0.3 mg/kg during induction only).
[a]Vasopressor: ephedrine 8–12 mg when mean arterial pressure reduction was more than 20% of baseline value.

Table 3. A comparison of neuromuscular blockade degree, neural monitoring recordings and postoperative adverse events (clinical application).

	Sugammadex (S Group, $n = 40$)	Conventional (C group, $n = 40$)	P value
V_1 stimulation			
Time from anesthesia (minutes)	44.6 ± 11.1	42.1 ± 13.9	0.39
EMG amplitude (μV)	1214 ± 623	915 ± 476	0.02
TOF ratio (%)	58.7 ± 17.1	44.9 ± 20.1	0.002
V2 stimulation			
Time from anesthesia (minutes)	83.2 ± 17.0	76.3 ± 18.2	0.09
EMG amplitude (μV)	1299 ± 651	1103 ± 438	0.13
TOF ratio (%)	85.2 ± 13.9	83.9 ± 12.2	0.69
Extubation time	4.7 ± 11.5	4.8 ± 9.9	0.88

EMG = electromyography, TOF = train of four, V_1= initial vagal stimulation.
V_2= final vagal stimulation, S group (rocuronium 0.6 mg/kg during induction, and sugammadex 0.5 mg/kg 10 minutes after skin incision), C group (rocuronium 0.3 mg/kg during induction only)..

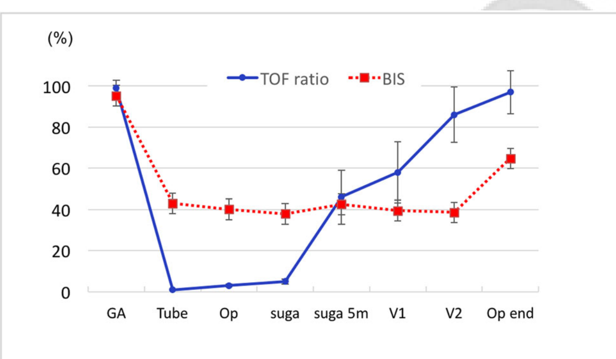

Figure 4. Time course of precision anesthesia protocol including neuromuscular transmission and anesthesia depth (clinical application). Neuromuscular transmission was monitored by train-of-four (TOF) ratio and anesthesia depth was assessed by bispectral index (BIS) derived from electroencephalogram (EEG).
GA = General anesthesia induction
Tube = Tracheal intubation of EMG tube
Op = Operation beginning
Suga = Intravenous injection sugammadex 0.5mg/kg at 10 minutes after operation
Suga 5m = Five minutes after sugammadex injection
V1 = initial vagal stimulation (44.6 ± 11.1 min from anesthesia)
V2 = final vagal stimulation (83.2 ± 17.0 min from anesthesia)

amplitude might be undetectable or markedly low when nerve stimulation is performed during surgical steps.[29,30]

Several feasible NMB regimens for monitored thyroidectomy have been proposed. The goals of optimal NMB for monitored thyroidectomy should provide not only excellent relaxation for tracheal intubation and surgical procedure but also rapid recovery of neuromuscular transmission for neural monitoring when nerve stimulation is tested. The combination of rocuronium and sugammadex is one of the solutions to ensure intubation condition, surgical relaxation and timely neuromuscular function recovery.[12,17,18] Sugammadex is a modified γ-cyclodextrin developed to selectively bind amino-steroidal NMBAs (i.e., rocuronium) but not isoquinoline NMBAs (i.e., cisatracurium).[31–33] Sugammadex reverses rocuronium-induced NMB more effectively than cholinesterase inhibitors (i.e., neostigmine); hence, it archives faster extubation after surgery and less postoperative residual curarization.[34]

Sugammadex dosage to prevent postoperative residual curarization is well defined according to peripheral nerve response (TOF ratio). During monitored parotid or thyroid surgery, a dose of 2 mg/kg sugammadex could induce nearly complete NMB recovery within 10 minutes.[17,19] Since muscle relaxation is also required during surgery, complete neuromuscular function recovery may not be the best management protocol. The main purpose of this study was to investigate suitable dosage and timing of sugammadex administration. We confirmed that low-dose sugammadex (0.5 mg/kg) was effective for obtain an excellent EMG response at the first vagus nerve stimulation (V1) in both porcine model and clinical application. Mean time required to obtain 50% recovery of EMG signal in piglets was 16.8 minutes. In the human surgical setting, the timing of sugammadex administration was designed at 10 minutes after skin incision. On an average, initial vagal stimulation V_1 was obtained at 28.5 minutes after skin incision. This duration ranged variously from 11 to 55 minutes. Our hospital served as a referral center and received patients with higher surgical difficulty such cancer, large goiter or repeated surgery. Those surgical steps required much more time than common thyroid surgery. The protocol showed that partial recovery of neuromuscular function (averaged TOF >58%) was feasible for high-quality V_1 EMG signal (mean amplitude 1214 μV with standard waveform) during monitored thyroidectomy.

Vagus nerve stimulation and obtain an initially satisfactory V_1 baseline EMG signal is a mandatory part for accurate neural monitoring during thyroid surgery.[1,3,10,28,35] Few studies have been proposed to apply sugammadex in IONM to avoid interference by NMB. Empis and coworkers proposed to use sugammadex in limited circumstances, they used it in only 12.5% (15/120) of patients whose EMG amplitude was less than 100 μV at V1 stimulation.[18] This selective neuromuscular recovery protocol could meet the neural monitoring demand and be more cost-effective than routine sugammadex use. From the surgeon's perspective, a higher EMG signal is generally requested for better decision-making; however, a notable weakness of the protocol was that all patients in general had relatively low V1 signal with medium and lowest EMG amplitude being 402.5 and 214.5 μV respectively. Medium and lowest EMG amplitudes were 522 and 180 μV for obese population respectively. Conversely, when routine sugammadex was used, EMG amplitude of V_1 signal was much higher and stable at a mean value above 1,200 μV in this study and in a previous report.[17]

To compare cost-effectiveness between sugammadex and neostigmine, two issues about neural monitoring and residual neuromuscular block were addressed. To facilitate intraoperative neural monitoring, sugammadex is superior to neostigmine. In our results, sugammadex even in smaller dose could restore adequate neuromuscular transmission to obtain high-quality EMG signal. Conversely, neostigmine could not be effective in fastening neuromuscular transmission recovery because TOF ratio is usually nearly zero at the time of skin incision. The drawback of sugammadex is the high cost approximately 100 USD per vial. To avoid postoperative residual neuromuscular block, sugammadex is not mandatory. Since merely single dose of NMBA is administrated, adequate neuromuscular transmission recovery is usually observed at the end of surgery. Therefore, neostigmine is probably fast enough in day-to-day anesthesia practice for conventional group.

Post-operaitve adverse events may have an impact on patient experience to surgery and anesthesia. To mitigate postoperative nausea, vomiting and pain, an anesthesia regimen was recommended to combine dexamethasone, propofol target-controlled infusion, parecoxib or NSAID and avoid postoperative opioids such as morphine.[12]

The current investigated protocol has several limitations. Firstly, only a small number of piglets were used. A well-established porcine model was used in the study. This widely applied protocol may enhance overall efficacy by following the replacement, reduction and refinement (3 R) principles in IONM studies.[22] We found that the results were highly reproducible in this study, hence, we believed that the data from the small number of piglets was sufficient. Secondly, the clinical trial was a retrospective study rather than a prospective, randomized study. The physical status of population in this trial was relatively healthy and patients with severe comorbidities were not enrolled in the study. The mean weight of all operated patients is about 64 kg. The reversal time of NMB with sugammadex in obese or morbidly obese is still matter of debate. Furthermore, the use of sugammadex is not recommended in renal failure patients even with dialysis. We did not include extreme elderly and pediatric population which may affect reversal time. Hence, our result demonstrates a feasible protocol only for non-obese adult population without renal failure. Thirdly, we focus on titrating neuromuscular blocking agent to optimize neural monitoring as well as anesthesia protocol, we did not analyze the impact of this protocol on mapping of the abnormal situations in RLN or EBSLN. However, our result showed that the precise NMB management ensured timely neuromuscular function restoration for high-quality EMG signal. Thus, the benefit and efficiency of precise NMB management on facilitating neural mapping of the abnormal situations in RLN or EBSLN deserve further investigation. Finally, concerning expenditure in healthcare system, protocol including sugammadex is a high-cost therapy and of restrictive use in most countries currently. Conversely, a less expensive and ultra-short acting NMBA-succinylcholine remains a choice for neural monitoring anesthesia. The only clinical caution is its rare side effects such as trismus, bronchospasm and malignant hyperthermia.

In conclusion, both porcine model and clinical application showed that precision NMB management by low-dose sugammadex was effective for IONM. There are some major advantages of precision NMB management for monitored thyroidectomy. Firstly, it allowed for adequate rocuronium dose to induce excellent tracheal intubation condition for EMG tube placement. Secondly, though low-dose sugammadex (0.5 mg/kg) only provided only partial neuromuscular function restoration, it still facilitated high-quality IONM (V_1) signal in a timely manner. Finally, a separate dose of sugammadex (1.5 mg/kg) at the end of surgery ensured safe and rapid extubation by complete neuromuscular function recovery. Therefore, we suggest including sugammadex administration into anesthesia strategy for IONM protocol to meet both anesthesia and surgery demands.

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Disclosure statement

The authors have no financial interests or conflicts of interest to declare.

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References

1. Randolph GW, Dralle H, Abdullah H, International Intraoperative Monitoring Study Group, et al. Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. *Laryngoscope*. 2011;121 (Suppl 1):S1–S16. doi:10.1002/lary.21119.
2. Barczyński M, Randolph GW, Cernea CR, International Neural Monitoring Study Group, et al. External branch of the superior laryngeal nerve monitoring during thyroid and parathyroid surgery: International Neural Monitoring Study Group standards guideline statement. *Laryngoscope*. 2013;123 (Suppl 4):S1–S14. doi:10.1002/lary.24301.
3. Schneider R, Randolph GW, Dionigi G, et al. International neural monitoring study group guideline 2018 part I: staging bilateral thyroid surgery with monitoring loss of signal. *Laryngoscope*. 2018;128 (Suppl 3):S1–s17. doi:10.1002/lary.24301.
4. Wu CW, Dionigi G, Barczynski M, et al. International neuromonitoring study group guidelines 2018: Part II: optimal recurrent laryngeal nerve management for invasive thyroid cancer-incorporation of surgical, laryngeal, and neural electrophysiologic data. *Laryngoscope*. 2018;128 (Suppl 3):S18–S27. doi:10.1002/lary.27360.
5. Zhang D, Wang T, Zhao Y, et al. Pre-prototype stimulating and recording endotracheal tube for continuous monitoring of the recurrent laryngeal nerve during thyroid surgery. *J Investig Surg*. Q3 2020;:1–11.
6. Ji YB, Ko SH, Song CM, et al. Feasibility and efficacy of intraoperative neural monitoring in remote access robotic and endoscopic thyroidectomy. *Oral Oncol*. 2020;103:104617. doi:10.1016/j.oraloncology.2020.104617.
7. Barczynski M. A novel approach to continuous monitoring of the recurrent laryngeal nerve during thyroid surgery. *Journal of Investigative Surgery: The Official Journal of the Academy of* Q4 *Surgical Research*. 2020;:1–2.
8. Dionigi G, Wu CW, Kim HY, Rausei S, Boni L, Chiang FY. Severity of recurrent laryngeal nerve injuries in thyroid surgery. *World J Surg*. 2016;40(6):1373–1381. doi:10.1007/s00268-016-3415-3.
9. Gurleyik E, Gurleyik G. Intraoperative monitoring of external branch of the superior laryngeal nerve: functional identification, motor integrity, and its role on vocal cord function. *J Invest Surg*. 2018;31(6):509–514. doi:10.1080/08941939.2017.1362489.
10. Wu CW, Lee KD, Tae K, et al. Recurrent laryngeal nerve (RLN) injury in thyroid surgery: lessons learned from the intraoperative neural monitoring (IONM). *International Journal of Head and Neck Science*. 2017;1(1):19–26.
11. Wu CW. Investigation the role of thyroid isthmusectomy for solitary isthmic papillary thyroid carcinoma. *Journal of Investigative Surgery: The Official Journal of the Academy of Surgical Research*. 2020;:1–2. Q5
12. Lu IC, Lin IH, Wu CW, et al. Preoperative, intraoperative and postoperative anesthetic prospective for thyroid surgery: what's new. *Gland Surg*. 2017;6(5):469–475. doi:10.21037/gs.2017.05.02.
13. Han YD, Liang F, Chen P. Dosage effect of rocuronium on intraoperative neuromonitoring in patients undergoing thyroid surgery. *Cell Biochem Biophys*. 2015;71(1):143–146. doi:10.1007/s12013-014-0176-1.
14. Chang PY, Wu CW, Chen HY, et al. Influence of intravenous anesthetics on neuromonitoring of the recurrent laryngeal nerve during thyroid surgery. *Kaohsiung J Med Sci*. 2014;30(10):499–503. doi:10.1016/j.kjms.2014.05.009.
15. Lu IC, Chu KS, Tsai CJ, et al. Optimal depth of NIM EMG endotracheal tube for intraoperative neuromonitoring of the recurrent laryngeal nerve during thyroidectomy. *World J Surg*. 2008;32(9):1935–1939. doi:10.1007/s00268-008-9549-1.
16. Stefanov CS, Dimov RS, Doikov IY, Konsulov SS. Method of anaesthesia in thyroid surgery with intraoperative monitoring of the recurrent laryngeal nerves. *Folia Med (Plovdiv))*. 2001;43(4):14–18.
17. Lu IC, Wu CW, Chang PY, et al. Reversal of rocuronium-induced neuromuscular blockade by sugammadex allows for optimization of neural monitoring of the recurrent laryngeal nerve. *Laryngoscope*. 2016;126(4):1014–1019. doi:10.1002/lary.25577.
18. Empis de Vendin O, Schmartz D, Brunaud L, Fuchs-Buder T. Recurrent laryngeal nerve monitoring and rocuronium: A selective Sugammadex reversal protocol. *World J Surg*. 2017;41(9):2298–2303. doi:10.1007/s00268-017-4004-9.
19. Lu IC, Chang PY, Su MP, et al. The feasibility of sugammadex for general anesthesia and facial nerve monitoring in patients undergoing parotid surgery. *Kaohsiung J Med Sci*. 2017;33(8):400–404. doi:10.1016/j.kjms.2017.06.002.
20. Brunaud L, Fuchs-Buder T. In reference to Reversal of rocuronium-induced neuromuscular blockade by Sugammadex allows for optimization of neural monitoring of the recurrent laryngeal nerve. *Laryngoscope*. 2017;127(1):E50doi:10.1002/lary.25990.
21. Lu IC, Wu CW, Chang PY, et al. In response to Reversal of rocuronium-induced neuromuscular blockade by sugammadex allows for optimization of neural monitoring of the recurrent laryngeal nerve. *Laryngoscope*. 2017;127(1):E51–E52. doi:10.1002/lary.26036.
22. Wu CW, Huang TY, Chen HC, et al. Intra-operative neural monitoring of thyroid surgery in a porcine model. *JoVE*. 2019;(144) doi:10.3791/57919. Q6
23. Lu IC, Chang PY, Randolph GW, et al. Safety of high-current stimulation for intermittent intraoperative neural monitoring in thyroid surgery: a porcine model. *Laryngoscope*. 2018;128(9):2206–2212. doi:10.1002/lary.27086.
24. Wu CW, Lu IC, Randolph GW, et al. Investigation of optimal intensity and safety of electrical nerve stimulation during intraoperative neuromonitoring of the recurrent laryngeal nerve: a prospective porcine model. *Head Neck*. 2010;32(10):1295–1301. doi:10.1002/hed.21324.
25. Wu C-W, Randolph GW, Lu I-C, et al. Intraoperative neural monitoring in thyroid surgery: lessons learned from animal studies. *Gland Surg*. 2016;5(5):473–480. doi:10.21037/gs.2016.09.06.
26. Wu C-W, Liu X, Barczyński M, et al. Optimal stimulation during monitored thyroid surgery: EMG response characteristics in a porcine model. *The Laryngoscopes*. 2017;127(4):998–1005. doi:10.1002/lary.26141.
27. Chiang FY, Lu IC, Kuo WR, Lee KW, Chang NC, Wu CW. The mechanism of recurrent laryngeal nerve injury during thyroid surgery-the application of intraoperative neuromonitoring. *Surgery*. 2008;143(6):743–749. doi:10.1016/j.surg.2008.02.006.
28. Chiang FY, Lee KW, Chen HC, et al. Standardization of intraoperative neuromonitoring of recurrent laryngeal nerve in thyroid operation. *World J Surg*. 2010;34(2):223–229. doi:10.1007/s00268-009-0316-8.
29. Lu IC, Tsai CJ, Wu CW, et al. A comparative study between 1 and 2 effective doses of rocuronium for intraoperative neuromonitoring during thyroid surgery. *Surgery*. 2011;149(4):543–548. doi:10.1016/j.surg.2010.11.006.

30. Marusch F, Hussock J, Haring G, Hachenberg T, Gastinger I. Influence of muscle relaxation on neuromonitoring of the recurrent laryngeal nerve during thyroid surgery. *Br J Anaesth*. 2005; 94(5):596–600. doi:10.1093/bja/aei110.
31. Puhringer FK, Gordon M, Demeyer I, et al. Sugammadex rapidly reverses moderate rocuronium- or vecuronium-induced neuromuscular block during sevoflurane anaesthesia: a dose-response relationship. *Br J Anaesth*. 2010;105(5):610–619. doi:10.1093/bja/aeq226.
32. Yang LP, Keam SJ. Sugammadex: a review of its use in anaesthetic practice. *Drugs*. 2009;69(7):919–942. doi:10.2165/00003495-200969070-00008.
33. Suy K, Morias K, Cammu G, et al. Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent. *Anesthesiology*. 2007;106(2):283–288. doi:10.1097/00000542-200702000-00016.
34. Carron M, Zarantonello F, Tellaroli P, Ori C. Efficacy and safety of sugammadex compared to neostigmine for reversal of neuromuscular blockade: a meta-analysis of randomized controlled trials. *J Clin Anesth*. 2016;35:1–12. doi:10.1016/j.jclinane.2016.06.018.
35. Wu CW, Chen CC, Wang MH, Huang TY, Chiang FY, Dionigi G. Recent advances in analysis and management of loss of signal during monitored thyroidectomy. *International Journal of Head and Neck Science*. 2018;2(4):147–155.