Feasibility of Intraoperative Neuromonitoring during Thyroid Surgery after Administration of Sugammadex for Reversal of Neuromuscular Blockade

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Abstract
Background Neuromuscular blocking agent (NMB) dosage suggested in current intraoperative neural monitoring (IONM) clinical guideline might cause operational difficulty during thyroid surgery. This study evaluated the feasibility of sugammadex with an enhanced NMB recovery protocol.

Methods Complete IONM data for 57 patients who had normal cord mobility were investigated: 32 patients received rocuronium 0.6 mg/kg at anesthesia induction and sugammadex 2 mg/kg at vagus nerve exposure (group S) and 25 received rocuronium 0.3mg/kg with 0.9% NaCl 2mL/kg instead (group R). Electromyography (EMG) signals were obtained from the vagus nerve and RLN before and after resection of the thyroid lobe and were defined as V1, V2 and R1, R2 signals, respectively. The train-of-four ratio (TOFr) was used for continuous quantitative monitoring of neuromuscular transmission.

Results Mean EMG in Group S (vagus nerve: 722.728 ± 160.11μV, RLN: 1028.64 ± 180.34μV) was greater than Group R (568.884 ± 135.15, 776.66 ± 145.91μV) from first minute after administration of sugammadex (P <0.05). The time for tracheal intubation was 102.97±64.5 seconds in group S with high dose rocuronium, while 195.12±68.9 seconds in group R (p < .001).

Conclusions Rocuronium 0.6 mg/kg can greatly shorten the tracheal intubation time and reduce the difficulty of surgery, and employment sugammadex can reverse residual muscle relaxation of rocuronium and optimize IONM conditions.

Background
Recurrent laryngeal nerve (RLN) palsy is one of the most common and dreaded complication after thyroid surgery. The indications to thyroid surgery and the extent of the initial thyroid resection influence postoperative outcomes. Intraoperative neuromonitoring (IONM) has been proposed to reduce the risk of RLN injury. The prevalence of using IONM during thyroidectomy is attributed to its two benefits: to verify the functional integrity of RLN during thyroid surgery, and to aid surgeon in RLN localization before visualization during operations, especially for high-risk situations, like re-operative settings and malignant disease surgery.

Neuromuscular blocking agents (NMBAs) are used during thyroid surgery to improve surgical
exposure. However, the administration of NMBAs might cause unsuccessful monitor during operation. Currently, sugammadex, an alternative to the conventional decurarisation traditionally performed with cholinesterase inhibitors, has been reported to be an effective and safe reversal of rocuronium-induced neuromuscular block at extubation [1-3].

Intraoperative administration of sugammadex might provide favorable recovery of NMB to facilitate IONM. Lu et al [4] reported that at the beginning of thyroid surgery, rocuronium 0.6 mg/kg was used for anesthesia induction and sugammadex 2 mg/kg allowed effective and rapid restoration of neuromuscular function. A retrospective cohort study showed a selective neuromuscular block recovery approach was reliable for intraoperative neuromonitoring [5]. Our prospective study is aimed to assess the use of intraoperative sugammadex during thyroid surgery by comparison of EMG signals with an enhanced NMB recovery protocol in order to provide a better anesthesia management for IONM in thyroid cancer surgery.

Methods
The study was approved by Fudan University Shanghai Cancer Center and the Chinese Clinical Trials.org (http://www. http://www.chictr.org.cn/; identifier: ChiCTR1800015797). The criterion is not applicable for this study. From January 2018 to July 2018, 57 patients (9 men, 48 women) aged 23 to 64 years (mean 42.42 years) undergoing radical thyroidectomy for thyroid cancer were included. Exclusion criteria included anticipated difficult intubation, severe liver or renal function impairment, asthma, drug abuse, morbid obesity, neuromuscular disease, and the use of medication that would influence neuromuscular transmission. One day before surgery, written informed consent was requested.

Preoperative hospital records, age, sex, body mass index (BMI, kg/m²), comorbidities, laboratory results and ultrasonographic findings were retrospectively recorded. Surgery type, IONM usage, RLN visualization, time of tracheal intubation, TOFr, intraoperative body movement, drainage usage, and operation time were recorded intraoperatively. The duration of hospital stay, complications, pathological results, and postoperative vocal cord mobility were recorded postoperatively.

All patients received routine monitoring such as noninvasive blood pressure, electrocardiogram,
oxygen saturation (SpO₂), anesthesia depth (Narcotrend) and TOFr. Anesthesia was induced with midazolam (0.05 mg/kg), propofol (2 mg/kg), sufentanil (0.3 µg / kg), and rocuronium (group S 0.6 mg/kg, group R 0.3 mg/kg). A 6- or 7-mm EMG endotracheal tube was used for women and men, respectively. The tube was placed with the middle of the exposed electrodes in contact with the true vocal cords under glidescope video laryngoscope. After confirming adequate placement of the nerve monitoring tube, IONM in the stand by state was ensured. Simultaneously, mechanically controlled ventilation was initiated. The anesthesia state was maintained with sevoflurane and remifentanil, and the Narcotrend was maintained at 45-64.

Thirty-two patients received an enhanced NMB recovery protocol—rocuronium 0.6 mg/kg at anesthesia induction and sugammadex 2 mg/kg upon exposure of the vagus nerve (group S); twenty-five patients received an induction dose of rocuronium 0.3 mg/kg at anesthesia induction and 0.9% NaCl 2 mL/kg at exposure of the vagus nerve (group R). During operation, standardized IONM procedures[6] were routinely followed, and the largest EMG amplitudes (V1 signal, vagal stimulation after the lateral space between the thyroid and the carotid sheath was opened and before any thyroid dissection; R1 signal, RLN stimulation at first identification; R2 signal, RLN stimulation after complete dissection; and V2 signal, repeat vagal stimulation after resection of the thyroid) were captured, registered, and compared.

As soon as the nerve was exposed, basic electrical signals were recorded for both group S and group R. In group S sugammadex was immediately administered at 2 mg/kg, while 0.9% NaCl was administered at 2 mL/kg in group R. To obtain the EMG response, the vagus nerve was touched directly by a monopolar nerve stimulator wand that was set at 2 mA (the stimulating current of 2 mA ensures a supramaximal stimulation of the vagus nerve). Then we recorded the electrical signals of vagal nerve and recurrent laryngeal nerve respectively 1, 2, 3, 5 minutes after sugammadex /0.9% NaCl injection as well as when the thyroid specimen was removed. The intubation time and body movement were also recorded in the two groups.

Statistical analysis of continuous variables (such as EMG amplitude, TOFr, time of tracheal intubation, intraoperative body movement, patients’ age, height, weight and body mass index) between group S
and group R was analyzed using unpaired student's t-test. Categorical nominal variables such as patients’ sex were compared with the chi-square test. P < 0.05 was considered as statistically significant and all statistical tests were 2-tailed. Data were presented as mean ± standard deviation.

Simple linear regression was performed to analysis the relationship between EMG amplitudes after resection of the thyroid lobe and mean EMG amplitudes during surgery for both signals obtained from the vagus nerve and RLN, and equation was expressed if linear relationship was revealed. One-way repeated measures analysis of variance was performed to analyze the EMG amplitudes under RLN and vagus nerve stimulation during different times in group S before and after administration of sugammadex.

Results

V1, V2 and R1, R2 were successfully obtained from all patients, and complete intraoperative neural monitoring data for 57 patients (32 in group S and 25 in group R) were recorded and analyzed. A comparison of the patients’ characteristics between group S and group R was shown in Table 1. No significant differences existed between two groups in terms of age, sex, height, weight and body mass index (BMI).

| Characteristic | Rocuronium (Group R) | Sugammadex (Group S) | p   |
|----------------|----------------------|----------------------|-----|
| Age (years)    | 42.4(26–63)          | 42.44(23–64)         | 0.123|
| Sex (no.)      |                      |                      |     |
| Female         | 20(80%)              | 28(87.5%)            | 0.441|
| Male           | 5(20%)               | 4(12.5%)             |     |
| Height (cm)    | 165.32(156–178)      | 161.47(154–177)      | 0.111|
| Weight (kg)    | 62.16(49–86)         | 59.88(46–110)        | 0.852|
| BMI            | 22.68(17.57–27.76)   | 22.94(16.85–40.4)    | 0.329|
| Tumor Size (no.) |                   |                      |     |
| < 1 cm         | 18(72%)              | 18(56.3%)            | 0.221|
| >=1 cm         | 7(28%)               | 14(43.7%)            |     |
| Tumor Location (no.) |          |                      | 0.61|
| Left           | 11(44%)              | 10(31.2%)            |     |
| Right          | 10(40%)              | 16(50%)              |     |
| Both Side      | 4(16%)               | 6(18.8%)             |     |

In group S, a linear relationship was observed between the EMG amplitudes after resection of the thyroid lobe (V2, R2) and the mean EMG amplitudes during surgery (V1, R1) for both signals were obtained from the vagus nerve (y = 1.94² + 0.71x) and the RLN (y = 2.97² + 0.61x). The graphs and linear relationship of vagus nerve and RLN are shown in Fig 1a and Fig 1b respectively. In group S,
higher EMG signals were obtained from 31 of 32 patients 1 minute after administration of sugammadex, and the relationships between EMG signal amplitudes and measurement time of vagus nerve and RLN are shown in Fig 2a and Fig 2b respectively. The mean EMG amplitude under RLN stimulation at 0, 1, 2, 3, 5 minutes and after thyroid lobe resection, was: 690.044 ± 121.881 μV, 1016.8 ± 200.816 μV, 1083.739 ± 217.272 μV, 1068.611 ± 206.928 μV, 993.194 ± 178.348 μV and 891.817 ± 129.574 μV for group S; and 820.06 ± 110.227 , 773.6 ± 103.131 , 762.733 ± 101.437 , 766.093 ± 99.755 , 754.093 ± 99.656 , 807.413 ± 116.569 for group R. The highest amplitude was obtained during the second minute after administration of sugammadex. The mean EMG amplitude under vagus nerve stimulation at 0, 1, 2, 3, 5 minutes and after thyroid lobe resection, respectively, was: 495.125 ± 97.457 μV, 696.427 ± 129.809 μV, 755.349 ± 139.831 μV, 767.396 ± 158.067 μV, 686.906 ± 138.024 μV and 707.563 ± 109.907 μV for group S; and 580.68 ± 75.106 μV, 572.293 ± 76.313 μV, 574.653 ± 79.635 μV, 548.48 ± 72.37 μV, 563.573 ± 84.809 μV, 585.42 ± 85.477 μV for group R. The highest amplitude was obtained during the third minute after administration of sugammadex. The mean amplitude in group S (vagus nerve: 722.728 ± 160.11μV, RLN: 1028.64 ± 180.34μV) was greater than in group R (vagus nerve: 568.884 ± 135.15 μV, RLN: 776.66 ± 145.91μV) from the first minute after administration of sugammadex (P <0.05) (Fig 2).

The impact of neuromuscular blockade reversal on surgery between the group using rocuronium with sugammadex (group S) and the group using rocuronium only (group R) was displayed in Table 2.

During surgery, the time of tracheal intubation was significantly lower in group S than in group R (102.97 ± 64.5 seconds vs. 195.12 ± 68.9 seconds; P < .001).

| Clinical Parameter | Rocuronium (Group R) | Sugammadex (Group S) | p |
|--------------------|----------------------|----------------------|---|
| Tracheal Intubation (s) | 195.12 ± 68.9 | 102.97 ± 64.5 | < .001 |

The related TOF and TOFr (TOF ratio, T4/T1) are shown in Fig. 3 and Fig. 4. The median of TOF reached 4 only at 1 minute after sugammadex injection. TOFr reached 52% at 1 minute and increased up to 5 minutes after sugammadex injection. Intraoperative body movement was significantly higher in group R (3/25) than in groups S (0/32) (P < 0.05). All patients had normal vocal mobility confirmed by
postoperative laryngeal fiberoptic examination. No equipment setup problem was experienced in this study.

Discussion
IONM as an adjunct technology can help thyroid surgeons track neurophysiologic changes of the RLN and elucidate mechanisms of injury that would not otherwise be interpreted anatomically. IONM has been applied to verify the functional integrity of RLN during thyroid surgery for decades and can also detect the nonrecurrent laryngeal nerve before RLN dissection during thyroid lobectomy[7]. However, the need for troubleshooting and the variable false IONM results still remain and hinder the application of this valuable technology. In the literature, the reported rate of unsuccessful neuromonitoring ranges from 3.8–23%[8-11]. The negative predictive value of IONM has been reported to be extremely high (range, 92–100%), but its positive predictive value was highly variable (range, 10–90%) [12, 13].

NMBAs are classified as competitive (nondepolarizing) and noncompetitive (depolarizing) inhibitions of neuromuscular transmission. Persisting neuromuscular blockade may affect the quality of IONM. To obtain ideal IONM signals, it is reasonable to assume that a depolarizing NMBAs (succinylcholine) with an extremely short duration might be better than any of the available nondepolarizing NMBAs. However, a nondepolarizing NMBAs such as rocuronium might be better than a depolarizing NMBAs with respect to patient safety. Previous study showed that patients who received rocuronium 0.6 mg/kg at induction, the rate of positive EMG response from initial vagal nerve stimulation was only 53%[14] and the mean EMG amplitude was markedly lower during the whole course of the operation. Therefore, a standardized setup protocol and an ideal control of NMBAs use might turn IONM into a more beneficial and reliable system.

In our study, a dose of rocuronium 0.6 mg/kg was used at anesthesia induction and sugammadex 2 mg/kg was used at the exposure of vagus nerve (group S) and group R received an induction dose of rocuronium 0.3 mg/kg at anesthesia induction with 0.9% NaCl 2 mL/kg upon exposure of the vagus nerve. The EMG amplitude captured before induction of sugammadex/0.9% NaCl (0 minute) was much lower in group S than in group R. It confirmed that the incomplete metabolism of muscle relaxants
would reduce IONM operability. At 1 minute after sugammadex induction, EMG signals of group S showed a rapid increase while EMG amplitude of group R stayed the same level as in 0 minute. This rapid restoration for neuromuscular function showed that it was feasible to administrate sugammadex during surgery upon the request of performing IONM. Sugammadex reversed the residual muscle relaxation of rocuronium successfully and optimized the intraoperative nerve monitoring conditions. Thus, the implementation of the NMB recovery protocol provided a better anesthesia management and assured IONM in thyroid cancer surgery.

Our data showed that induction with 0.6 mg/kg rocuronium could shorten the intubation time than 0.3 mg/kg rocuronium and all patients experienced successful tracheal intubation at the first attempt. The time of tracheal intubation in group S was significantly lower than that in group R (Table 2) and sugammadex 2 mg/kg allowed effective and rapid restoration of neuromuscular function after rocuronium 0.6 mg/kg. According to the pharmacological characteristics of muscle relaxant, it was obvious that induction with 2 ED95 doses muscle relaxants can decrease the drug's initial efficacy time than that with only 1 ED95. As soon as 1 minute after sugammadex injection the TOF value arrived at 4 and after 5 minutes the TOFr rising to 98.85 ± 17.16%, which all made sure of continuous movement of the vocal cords, and that was the essential condition of IONM application. Instead, the TOFr of R group was only reaching 76.68 ± 12.72% after the removal of the tumor, which might illustrate that during the whole operation the IONM was affected by the effect of rocuronium. Moreover, intraoperative body movement was significantly lower in group S than in groups R (P < 0.05).

There are differences in the various kinds of anticholinesterase drugs used to antagonize the residual effects of nondepolarizing muscle relaxants. Using sugammadex can shorten the recovery time to a TOFr > 0.9 at the end of surgery. In the US, reversal therapy after anaesthesia is performed routinely, whereas, in some European countries, it is not a common practice. Reservations regarding the reversal of a competitive neuromuscular block with anticholinesterase agents stem from the possible side effects. In addition to the potential cardiovascular effects of atropine, glycopyrrolate, neostigmine, and edrophonium, neostigmine causes dry mouth, nausea, vomiting, bronchospasm,
and increased bowel movements[15].

Recently sugammadex, which is a specific cyclodextrin, has been developed to antagonize the neuromuscular block caused by steroidal neuromuscular blocking agents such as rocuronium and vecuronium[16–18]. Sugammadex works by quickly reducing the number of rocuronium molecules on the nicotinic receptors of the motor endplate by the rocuronium molecules in the plasma. Thus, it allows to conceal neuromuscular paralysis to facilitate endotracheal intubation and complete neuromuscular recovery shortly thereafter, thus allowing appropriate intraoperative neuromonitoring.

Neostigmine is not a direct pharmacological antagonist of NMBAs. Rather, neostigmine inhibits acetylcholine esterase. The accumulated acetylcholine then competitively displaces the NMBAs from the receptor. This is only effective when the NMBAs concentration in the neuromuscular junction has already decreased, that is, not at a profound deep neuromuscular block. In contrast, sugammadex chelates all the free NMBAs in the plasma quickly, thereby creating a large concentration gradient between the neuromuscular junction and the plasma for free NMBAs. The resulting diffusion of NMBAs from neuromuscular junction to plasma causes a drop in end plate occupancy of NMBAs which occurs much more quickly than after reversal by neostigmine[17, 19].

However, sugammadex is an expensive product and has restrictive use in some countries. A retrospective cohort study[5] showed fifteen (12.5%) patients needed sugammadex reversal to obtain an EMG response at V1 stimulation and suggested a selective neuromuscular block recovery approach may be valuable to an enhanced neuromuscular block recovery protocol. Meistelman et al.[20] reported that the blockade after a bolus dose of 0.5 mg/kg rocuronium was significantly less deep at the larynx muscles (77 ± 5%) compared to the adductor pollicis muscle (98% ±1%). A muscular response to RLN stimulation instead of complete adductor pollicis muscle recovery was needed to obtain reliable information for IONM. In this context, a selective neuromuscular block recovery protocol may be a suitable option.

In the clinical guidelines on intraoperative neuromonitoring, 1x ED95 intermediate-acting non-depolarizing muscle relaxant is recommended to avoid the influence of the muscle relaxant for IONM[21]. Lu et al. [14] reported that 30 min after an intubating dose of rocuronium (i.e. 0.6 mg/kg)
spontaneous recovery at the adductor muscles of the larynx was advanced, allowing a positive EMG signal from initial nerve stimulation in 53% of their patients. They found that 2 mg/kg sugammadex used for reversal NMBAs at the early stage of surgery allowed effective and rapid restoration of neuromuscular function deeply suppressed by rocuronium 0.6 mg/kg[4]. Our study demonstrated that, rocuronium 0.6 mg/kg with sugammadex upon exposure of the vagus nerve, allowed a high and intensity EMG signal in 1 minute after administration. The mean EMG amplitude under RLN stimulation and vagus nerve stimulation at first minute was 1016.8 ± 200.816 μV and 696.427 ± 129.809 μV, respectively, high enough for adequate IONM. It suggested that rocuronium 0.6 mg/kg with intraoperative 2 mg/kg sugammadex was feasible for IONM. With the larger doses of rocuronium, there would be many benefits for thyroid cancer surgery (thyroidectomy and lymph node dissection), such as shorter muscle relaxant onset time, shorter intubation time, decrease of intraoperative body movement and muscle twitches caused by electrosurgical devices, which could make the surgery more stable and safer, meanwhile the surgeon would get higher satisfaction. Thus, this enhanced NMB recovery protocol may optimize the muscle relaxant induction dose and provide a better anesthesia management for IONM in thyroid cancer surgery.

There were several limitations in this study. First, we used nondepolarizing NMBAs (rocuronium) in our daily practice. There was no other depolarizing group for controls. Second, the case number (n = 57) was slightly small. A larger number of cases is being conducted to demonstrate the standardized setup protocol and an ideal control of NMBAs and sugammadex use might turn IONM into a more beneficial and reliable system.

**Conclusion**

In conclusion, the induction dose of 0.6 mg / kg rocuronium is beneficial to tracheal intubation and surgery. During operation, sugammadex can reverse the residual muscle relaxation of rocuronium and optimize the intraoperative nerve monitoring conditions. The enhanced intraoperative NMB recovery protocol may provide a better anesthesia management for IONM in thyroid cancer surgery.

**Abbreviations**

RNL: Recurrent laryngeal nerve; IONM: Intraoperative neuromonitoring; NMBAs: Neuromuscular
blocking agents; BMI: body mass index; SpO2: oxygen saturation.

Declarations

**Ethics approval and consent to participate**

Ethical approval for this retrospective study (1909-021-1060) was approved by Fudan University Shanghai Cancer Center and the Chinese Clinical Trials.org (http://www.chictr.org.cn; identifier: ChiCTR1800015797). Written informed consent of patients was obtained. We also registered in ClinicalTrials.gov (ChiCTR1800015797).

**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

QHJ, YW and ZRS designed the study, collected, analyzed and interpreted the data and drafted the manuscript. SWY, XL, XYC and ZRS designed the study, analyzed and interpreted the data and critically revised the manuscript. QHJ, YW and ZRS designed the study, analyzed and interpreted the data, drafted and critically revised the manuscript. All authors read and approved the final manuscript.

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**Figures**

![Figure 1](image)

(a) The linear relationship between the EMG amplitudes after resection of the thyroid lobe and the mean EMG amplitudes during surgery for vagus nerve. (b) The linear relationship between the EMG amplitudes after resection of the thyroid lobe and the mean EMG amplitudes during surgery for RLN.
Figure 2
(a) The relationships between EMG signal amplitudes and measurement time for vagus nerve. Comparison of mean EMG amplitudes at each time point between two groups (p<0.05). (b) The relationships between EMG signal amplitudes and measurement time for RLN. Comparison of mean EMG amplitudes at each time point between two groups (p<0.05).

Figure 3
The TOF at each time point monitored.

Figure 4
The TOFr at each time point monitored.