THYROID SURGERY, IONM AND SUGAMMADEX SODIUM RELATIONSHIPS: BENEFITS IN SUGAMMADEX SODIUM USE FOR IONM

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Abstract

Background. It is important to protect recurrent laryngeal nerve (RLN) during thyroid surgery. Thus, intraoperative neuromonitoring (IONM) has got popularity. But, the half life of neuromuscular blocking agents used has a reverse correlation with reliability and effectiveness of IONM. This study aimed to research the effect of Sugammadex Sodium, a specific neuromuscular blocking agent antagonist, on nerve conduction and IONM.

Materials and methods. Twenty patients who underwent thyroidectomy under IONM followed an enhanced NMB recovery protocol-rocuronium 0.6 mg/kg at anesthesia induction and sugammadex 2 mg/kg at the beginning of operation. To prevent laryngeal nerve injury during the surgical procedures, all patients underwent intraoperative monitoring. At the same time, the measurement of TOF-Watch acceleromyograph of the adductor pollicis muscle response to ulnar nerve stimulation was performed; recovery was defined as a train-of-four (TOF) ratio ≥ 0.9 . Age, sex, recurrent laryngeal nerve transmission speeds prior to and after operation, BMI, duration of surgery, the change in nerve transmission after drug administration and complications were analyzed.

Results. The mean age and the mean BMI were 47.6 ± 11.82 years and 28.74 ± 3.20 , respectively. The mean operation duration was 52.65 ± 5.51 minutes. There was no difference in either right or left RLN monitoring values before and after surgery. Following the drug injection, the TOF guard measurements on the 1st, 2nd, 3rd and 4th minutes were 23.5 ± 4.90 ; 69.5 ± 6.86 ; 88 ± 4.1 and 135.9 ± 10.62 , respectively.

Conclusion. Neuromuscular blocking antagonist use and monitoring nerve transmission speed with TOF-guard can provide a safer resection.

Key words: thyroidectomy, intraoperative nerve monitoring, TOF guard.

INTRODUCTION

Thyroid resections might have severe complications because of its anatomic relations with critical structures. One of the severe complications of thyroid surgery is recurrent laryngeal nerve (RLN) paralysis (1, 2). The incidence of RLN paralysis varies between less than 1 percent and as high as 20 percent which depends on the type of disease (benign or malignant), the type of thyroid resection (first-time or re-operation), extent of surgery (subtotal or total thyroidectomy), mediastinal involvement, surgical technique (with or without routine RLN identification) and experience of the surgeon (3-5). RLN dysfunction is a severe complication resulting in voice loss, thus, social, psychological and work problems (6, 7).

Intraoperative identification and preservation of the RLN was proposed to be an integral part of thyroid surgery by Lahey in 1938 and has been demonstrated to decrease the incidence of postoperative nerve paralysis (6-9). The nerve identification has been proposed as gold standard (7, 9). RLN injury might occur even in experienced hands. The permanent and temporary nerve palsy incidences are reported as 2.3% and 9.8%, respectively (10). Despite the low rate of permanent RLN injury, this complication continues to be a problem for patients and surgeons and a frequent source of medical malpractice claims against surgeons as the leading cause of medico-legal litigation following endocrine surgery (8).

Intraoperative neuromonitoring (IONM) has been proposed as a complementary procedure to visual detection of superior and RLN in thyroid surgery which can provide a decreased injury risk (8). There are studies reporting that IONM is useful on detecting RLN (9). But, its usefulness in decreasing the nerve injury and in assessing the nerve function after operation is still controversial (6, 7, 9). Studies reported a high negative

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predictive value from 92 and 100% but a highly variable positive predictive value of 10-90% for IONM (11).

Non-depolarizing neuromuscular blocking (NMB) agents are used for easier intubation. Rocuronium and vecuronium are more commonly used NMB agents compared to succinylcholine which has potentially severe adverse effects. (12). Although they provide an easy intubation, they also cause loss of EMG signals, making IONM more difficult. Thus, NMB agent use in thyroid resections is controversial (6, 13-15). Peripheral nerve stimulation is used for evaluating the block reversal and tactile or optic response to the stimulation is followed. PNS monitoring for the drug reversal time might help in decreasing the emergence and intensity of persistent nerve paralysis. There are reports saying that TOF sequence, the ratio of the fourth response to the first should be 0.90, for a total recovery of NMB effect on pharyngeal and respiratory muscles (16, 17).

Sugammadex is an anti-NMB agent forming a complex with rocuronium and vecuronium, and it prevents them from binding to nicotinic cholinergic receptors at the myoneural junction (18). TOF response was used to evaluate its effectiveness on neuromuscular block reversal and sugammadex was shown to reverse the strong block within few minutes after its injection (16, 17, 19).

The aim of the present retrospective clinical study is to research nerve transmission by using TOF - Guard monitor and succeed in an accurate IONM by using NMB antagonist agent Sugammadex Sodium (Bridion).

PATIENTS AND METHODS

The thyroidectomy patients operated in the general surgery department between January 2016 and April 2017 were analyzed retrospectively. All operations were performed by experienced surgeons after obtaining a detailed informed consent. Twenty patients (16 female, 4 male) who underwent thyroidectomy because of multinodular goiter, nodular goiter, thyroid cancer, retrosternal goiter were included into the study. Informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. All patients underwent thyroid ultrasound, and thyroid disease was confirmed. Children, pregnant, mentally retarded patients and the patients with prior laryngeal surgical history were excluded.

All the patients were given intravenous

midazolam (maximum 2 mg) premedication in the operation room.

Vital signs of the patients were monitored continuously.

Oxygen was administered by mask before the general anesthesia was initiated and the anesthesia was induced with remifentanyl (target concentration of 1 ng/mL) for anesthesia induction; propofol bolus (2-3mg/kg), fentanyl (0.5-1µg/mL) and 0.6 mg/kg rocuronium intravenously were used for NMB. The anesthesia maintenance was done using sevoflurane (0.8 MAC) and remifentanyl (1.5-3µg /mL) infusion and a mixture of air / oxygen of 4 lt/min. No neuromuscular blocking agent was re-injected.

Following the anesthesia, the patient was ventilated for two minutes and intubated with an armored endotracheal tube (7 to 7.5 mm internal diameter) with a surface electrode fixed 2 cm superior to the cuff (Dr. Langer Laryngeal tube electrode). The adhesive electrodes, 6-7 or 7.7-9 mm size, were circularly wrapped around the endotracheal tube, 10-20 mm above the cuff (balloon), approximating vocal cords. The anesthesiologist checked if it was correctly placed by using a laryngoscope (Fig. 1, A-C). To prevent a short circuit and an adverse effect of the electrical current, a ground electrode was placed on the shoulder and connected to the laryngeal tube. The correct settlement of the electrodes around vocal cords was checked by recording motor action potential response in the neck to the electrical impulse on laryngeal nerve.

IONM was performed according to the International Neuromonitoring Study Group (INMSG) Guidelines (20). IONM system using voice alert and graphical presentation was used (Dr. Langer, Germany). After intubation, the TOF-Guard monitor electrode was put on left hand and TOF was measured and recorded (TOF-Watch SX (Schering-Plough, Dublin, Ireland)) (Fig. 1, D). The electrodes were located on the wrist and the ulnar nerve. The acceleromyographic transducer was fixed on the anterior face of the thumb tip, ulnar nerve was stimulated and *adductor pollicis* muscle response was measured.

Following anesthesia induction, a 5-second, 50-Hz tetanic stimulation of the ulnar nerve was used for stabilization of signal. After 1 minute, the fingers were fixed and TOF stimulation was given for 2 to 5 minutes. The TOF-Watch SX was calibrated and then repetitive TOF stimulation was started. 0.2 msec long, 2Hz TOF pulses were given at 15 seconds interval till taking the TOF ratio of 0.9.

A 3-to 4-cm Kocher incision was made and the

Figure 1. A-C: System of monitoring of the laryngeal nerve function with an adhesive laryngeal electrode that is directly attached on the ventilation tube (Dr. Langer electrode and intubation tube). D: TOF monitor device and PNS electrodes were positioned near the wrist and the ulnar nerve.

platysma with subplatysmal flaps were raised superiorly and inferiorly with the help of the electrocautery. The strap muscles were retracted for lateral exposure of the middle thyroid vein, if present, to be divided. All small vessels were occluded with a vessel-sealing device. The electrocautery was used to dissect the pyramidal lobe and the isthmus. During total thyroidectomy, the vagal nerve was found on the left side first. The vagus nerve was found by dissecting the area between carotid artery and jugular vein. The vagus nerve (VN) was identified under direct vision and the absence of the signal was observed. Then, a sugammadex sodium (2mg/kg) bolus was administered intravenously. Following sugammadex sodium injection, TOF records of 1st, 2nd, 3rd and 4th minutes were measured and at the point where the response was bigger than 90%, the neuromuscular monitoring device was started to be used.

The IONM technique had 4 phases: (1) VN stimulation before thyroid dissection (V1); (2) RLN stimulation when it is found (R1); (3) RLN stimulation after thyroid resection (R2); (4) VN stimulation when thyroidectomy was completed (V2). The V1 signal was considered positive when the wave amplitude was higher than 500 μ V. If there was no response to the first IONM stimulation or the signal was lower than 500 μ V, was used to antagonize NMB. Following sugammadex injection, the surgeon gave repeated IONM stimulations. It was accepted as technical failure of the IONM when there was no response after complete neuromuscular recovery. When V1 signal becomes positive (either by itself or by using sugammadex), surgical resection was begun. RLN was identified in the tracheoesophageal sulcus.

The first signal was taken when the RLN was found in tracheoesophageal sulcus and the last signal was taken following the complete resection. The RLN was checked by using 1mA stimulations. When two structures run close together (such as anterior

and posterior branches of the RLN, or a small artery and RLN), a false EMG signal might have been seen because of a shunt stimulus, the stimulation level was decreased to 0.5 mA. Stimulation interval for IONM was 1 second, therefore, the RLN and VN were monitored continuously. The initial baseline responses bigger than 500 μ V were desired, then lobectomy was performed under nerve monitoring and R2 and V2 values were measured after resection in both sides.

Statistics

SPSS for Windows (version 11, 0; SPSS, Chicago, IL) was used for statistical analysis. Results were given as the mean $\pm$ SD (for continuous variables) or percentage (for categorical variables). Comparisons between the groups were done by using t test for continuous variables and χ^2 test for categorical variables. P value of significance level was 0.05.

RESULTS

The patient demographics were given in Table 1. The mean age was 47.6 ± 11.82 years and mean BMI was 28.745 ± 3.20 kg/m². The mean operation time was 52.65 ± 5.51 (47-58) minutes. There was not any significant difference between the before and after the surgery values for right and left RLN, respectively ($p=0.291$, $p=0.363$) (Table 2).

Table 1. Patient characteristics

Variable	
Gender (no)(female/male)	16/4
Age (years)	47.6 ± 11.82
BMI (kg/m ²)	28.745 ± 3.20
ASA (I/ II)	11/9
Operation time (min)	52.65 ± 5.51

Data are presented as means $\pm$ SD or number of patients (no.), BMI body mass index, ASA: American Society of Anesthesiologist.

Table 2. The EMG amplitude values of RLN under neuromonitorization

	R1	R2	P value
Right RLN	827.79 μ V $\pm$ 277.320	840.83 μ V $\pm$ 288.085	0.291
Left RLN	667.96 μ V $\pm$ 112.065	689.17 μ V $\pm$ 137.932	0.323

RLN: Recurrent Laryngeal Nerve, R1:RLN stimulation at the initial identification, R2: RLN stimulation at the end of thyroid resection.

V0, V1 and V2 values were $82.15 \pm 8.39 \mu$ V; $786.64 \pm 134.27 \mu$ V and $912.24 \pm 156.24 \mu$ V, respectively.

TOF did not show any value for 1st and 2nd minutes but TOF ratio. It started to show a value at 3rd and 4th minutes meaning that TOF ratio of 4 was reached which was a value bigger than 0.9 (90%). When the TOF values were bigger than 0.9 at the 3rd and 4th minutes, the values bigger than 500 μ V on IONM were accepted significant. After reaching these values, RLN exploration was started and the operation was kept going on. Especially the values at the 4th minute showed that the effect of NMB drugs was reversed completely (Table 3).

Temporary RLN paralysis was seen in one patient and reversed completely at the end of two months. Two patients developed transient hypocalcemia which was also normalized on the 9th post operative week.

One patient developed hematoma which resolved spontaneously within 7 weeks without any intervention as confirmed by ultrasound. The patients developed neither permanent hypocalcemia nor RLN paralysis.

DISCUSSION

The most major complication of thyroid surgery is voice impairment because of RLN paralysis. Various methods and tools have been tried to prevent RLN paralysis. A good understanding of nerve anatomy, experience and training of surgeon and an increased number of nerve dissections are compulsory (1-5). Pre and post operative laryngoscopic examination of VCs for movement has been widely accepted (21). Intraoperatively, RLN has been recognized, exposed and today, its recognition and function are confirmed by using devices (4). New techniques and tools have been started to be used in thyroid surgery. Now a current approach consists of pre and post op laryngoscopy, direct visualization and dissection of RLN and evaluation of its function before, during and

after surgical resection (3,4,6-11).

Standardization of new technologic methods for being more accurate, safe, easily-applicable, reliable, acceptable and repeatable, is important for education and training and most appropriate results (22, 23). Such a standardized method in the light of guidelines provides an increased chance to detect and protect the RNL and if an injury occurs, it enables the surgeon to detect it during operation (10, 23). The main determinative impulse in thyroidectomy with IONM was V1 (11, 24). V1 enables us to discriminate and confirm the nerve, to make dissection, and it prevents visual misidentification. But, even if the RNL is not found by using V1, IONM can be performed for dissection and RLN identification (25-27). It was reported that standard (S-IONM) or continuous (C-IONM) can increase the nerve identification rate (25, 26).

IONM is used as an adjunct to direct visualization of the nerve, which is the gold standard, to prevent nerve injury (24). In the present study, we aimed the reversal of NMB on a specific group of muscles, laryngeal muscles by using IONM.

Lee *et al.* compared rocuronium/sugammadex sodium and succinyl choline in their prospective randomized series of 115 patients and reported that rocuronium/sugammadex group responded faster where sugammadex sodium dose was 16mg/kg (12). Pavoni used higher doses of sugammadex (16mg/7kg) for rocuronium reversal and suggested it (17).

Yamamoto *et al.* used 2mg/kg and 4mg/kg of sugammadex sodium, respectively in two groups, respectively, to reverse the effect of 1mg/kg rocuronium and recorded TOF responses and as the sufficient TOF responses could not be taken in group 1 where 2mg/kg sugammadex sodium was used and the dose was completed to 4mg/kg (28). In pigs, 2mg/kg and 4mg/kg sugammadex were used in two groups to antagonize the effect of 0.6 mg/kg rocuronium. They recorded vagus measurements at the beginning and ending,

Table 3. Times from sugammadex (2mg/kg) administration to start and total recovery after 4 minutes

	1 st min	2 nd min	3 rd min	4 th min
TOF value	1-2	69.5 $\pm$ 6.86	88 $\pm$ 4.1	135.9 $\pm$ 10.62
Nervus vagus signal (μ V)	149.46 μ V $\pm$ 51.346	334.76 μ V $\pm$ 86.114	786.64 μ V $\pm$ 134.27	894.36 μ V $\pm$ 151.435

Data are presented as means $\pm$ SD, TOF: Train of four monitoring.

EMG values of identified RLN and verified the reversal of NMB by measuring TOF value of adductor pollicis muscle. They concluded that 2 mg/kg sugammadex was sufficient for a rapid and safe NMB reversal (15).

Sugammadex sodium has some side effects like pain (36-52%), nausea (23-26%), vomiting (11-15%), hypotension (4-13%), headache, (5-10%), pyrexia (5-9%) and hypertension (5-9%). We think that these side effects can be more commonly seen in high doses. The reports did not have any information on side effects. We observed headache in one patient and pyrexia because of allergic eruptions in another, respectively in our study. The dose suggested to reverse the effect of rocuronium is 2 mg/kg. 2 mg/kg sugammadex was sufficient for rapid reversal within a few minutes in all patients in our study.

International standard guideline suggests vagal stimulation and V1 measurement during thyroid operations (1). Taking optimal EMG signal is essential to find RLN and to prevent nerve injury (27, 29, 30).

In our study, sugammadex was administered 16 minutes after GA induction with rocuronium and all patients could be intubated at the first attempt and TOF ratio of >0.9 was taken within 4 minutes. V0 was the value taken before sugammadex sodium injection; V1 was the values at the 3rd and 4th minutes and V2 was the value taken after the lobectomy. The signal intensity on IONM might vary in every patient (24). The EMG signal might be affected by endotracheal tube location, gland manipulation, wet surgical field, bad probe-nerve contact and temperature (23, 31). These factors might explain the presence of big values for the standard deviation of the V1 and V2 signals in this study. The early antagonist effect of sugammadex with fast NMB reversal resulted in the V1 and V2 signal values to become closer to each other. It was reported that the reversal effect of sugammadex is correlated with dose and 2 to 4 mg/kg of the drug suffices for easy extubation (32).

We found V0 $82.15 \pm 8.39 \mu\text{V}$; V1 $786.64 \pm 134.27 \mu\text{V}$ and V2 $912.24 \pm 156.24 \mu\text{V}$. While the TOF response for the V0 was zero, the TOF response for V1 was found bigger than 90%. In spite of 3rd minute V values were higher than $500 \mu\text{V}$ in some patients, 4th minute-values were taken into account because TOF responses were less than 0.9. The provision of complete reversal in all the patients was proven with both TOF and V1 values. The incomplete reversal at the 3rd minute might be related to age, which was blamed of late reversal of NMB in some reports (17, 28).

The procedure can also help to detect the nonrecurrent laryngeal nerve during thyroid lobectomy (27, 29).

There are lots of studies comparing RLN paralysis incidence between IONM and direct nerve visualization. Barczynski *et al.* in their clinical series enrolling 1000 cases reported that the use of IONM decreased transient paralysis incidence but there was no difference between IONM use and direct nerve visualization in terms of permanent paralysis incidence (9, 33). Frattini *et al.* reported that IONM use significantly decreased both the transient and permanent RLN paralysis incidence compared to that of direct nerve visualization in 152 total thyroidectomy patients for thyroid cancer (33). Shindo *et al.*, in their retrospective analysis of 684 cases, did not find any difference between IONM and direct nerve visualization in terms of transient and permanent RLN paralysis (33). The meta-analysis on 16517 patients of twenty studies comparing nerve monitoring and direct looking for the nerve reported the RLN palsy as 3.47% and 3.67% for nerve monitoring and direct looking without any significant difference, respectively (33). The factors causing failure in decreasing the nerve palsy are either because of relying on the monitoring so much or false signals formed by vessels and bleeding are not clear (5,10). In our study, we observed that, in some, in spite of more than $500 \mu\text{V}$ V1 value, the TOF measurement was less than 0.9. As the TOF value below 0.9 showed incomplete reversal of NMB, the question brought into mind that a real complete IONM response was present in patients in whom RLN paralysis occurred? We had one transient RLN paralysis but no permanent one in our study.

The limit of our study was the small number of cases and absence of IONM control group for comparison. However, prospective randomized studies enrolling large number of cases are needed.

In conclusion, intravenous sugammadex in 2 mg/kg dose provides effective and rapid reversal of neuromuscular blockade caused by rocuronium used for intubation. The use of this NMB reversal provides both an easier both tracheal intubation and proper IONM during thyroid surgery.

The use of an NMB antagonist drug, sugammadex, and showing the nerve transmission by using a TOF-guard monitor can provide a more accurate IONM and safer surgery.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

1. Steurer M, Passler C, Denk DM, Schneider B, Niederle B, Bigenzahn W. Advantages of recurrent laryngeal nerve identification in thyroidectomy and parathyroidectomy and the importance of preoperative and postoperative laryngoscopic examination in more than 1000 nerves at risk. *Laryngoscope* 2002; 112: 124–133.
2. Neagoe RM, Cvasciuc IT, Muresan M, Sala DT. Incidental Parathyroidectomy During Thyroid Surgery - Risk, Prevention and Controversies; An Evidence-Based Review. *Acta Endocrinologica-Bucharest* 2017; 13:467–475.
3. Jatzko GR, Lisborg PH, Muller MG, Wette VM. Recurrent nerve paralysis after thyroid operations – principal nerve identification and a literature review. *Surgery* 1994; 115: 139–144.
4. Chiang FY, Wang LF, Huang YF, Lee KW, Kuo WR. Recurrent laryngeal nerve paralysis after thyroidectomy with routine identification of the recurrent laryngeal nerve. *Surgery* 2005; 137: 342–347.
5. Hermann M, Alk G, Roka R, Glaser K, Freissmuth M. Laryngeal recurrent nerve injury in surgery for benign thyroid diseases: effect of the nerve dissection and impact of individual surgeon in more than 27 000 nerves at risk. *Ann Surg* 2002; 235: 261–268.
6. Dralle H, Sekulla C, Lorenz K, Brauckhoff M, Machens A; German IONM Study Group. Intraoperative Monitoring of the Recurrent Laryngeal Nerve in Thyroid Surgery. *World J Surg* 2008; 32:1358–1366.
7. Chan WF, Lo CY. Pitfalls of Intraoperative Neuromonitoring for Predicting Postoperative Recurrent Laryngeal Nerve Function during Thyroidectomy. *World J Surg* 2006; 30:806–812.
8. Angelos P. Recurrent Laryngeal Nerve Monitoring: State of the Art, Ethical and Legal Issues. *Surg Clin N Am* 2009;89:1157–1169.
9. Barczyński M, Konturek A, Cichoń S. Randomized clinical trial of visualization *versus* neuromonitoring of recurrent laryngeal nerves during thyroidectomy. *Br J Surg* 2009;96:240–246.
10. Zheng, Xu Z, Wei Y, Zeng M, He J. Effect of intraoperative neuromonitoring on recurrent laryngeal nerve paralysis rates after thyroid surgery; a meta-analysis. *Journal of the Formosan Medical Association* 112.8. 2013: 463–472.
11. Chiang FY, Lee KW, Chen HC, Chen HY, Lu IC, Kuo WR, Hsieh MC, Wu CW. Standardization of Intraoperative Neuromonitoring of Recurrent Laryngeal Nerve in Thyroid Operation. *World J Surg* 2010; 34:223–229.
12. Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M. Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium. *Anesthesiology* 2009;110:1020–1025.
13. 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;94:596–600.
14. Wu C-W, Wang M-H, Chen C-C Hui-Chun Chen, Hsiu-Ya Chen, Jing-Yi Yu, Pi-Ying Chang, I-Cheng Lu, Yi-Chu Lin, Feng-Yu Chiang. Loss of signal in recurrent nerve neuromonitoring: causes and management. *Gland Surg* 2015;4:19–26.
15. Lu I-C, Wu C-W, Chang P-Y, Chen HY, Tseng KY, Randolph GW, Cheng KI, Chiang FY. Reversal of rocuronium- induced neuromuscular blockade by sugammadex allows for optimization of neural monitoring of the recurrent laryngeal nerve. *Laryngoscope* 2016;126:1014–1019.
16. Kopman, Zank LM, Ng J, Neuman GG. Antagonism of cisatracurium and rocuronium block at a tactile train-of-four count of 2: should quantitative assessment of neuromuscular function be mandatory? *Anesthesia & Analgesia* 98.1. 2004: 102–106.
17. Pavoni V, Giancesello L, Martinelli C, Horton A, Nella A, Gori G, Simonelli M, De Scisciolo G. Recovery of laryngeal nerve function with sugammadex after rocuronium-induced profound neuromuscular block. *J Clin Anesth.* 2016 ;33:14–19.
18. Kovac AL. Sugammadex: the first selective binding reversal agent for neuromuscular block. *J Clin Anesth* 2009;21:444–453.
19. Duvaldestin P, Kuizenga K, Saldien V, Claudius C, Servin F, Klein J, Debaene B, Heeringa M. A randomized dose-response study of sugammadex given for the reversal of deep rocuronium- or vecuronium-induced neuromuscular blockade under sevoflurane anesthesia. *Anesth Analg* 2010;110:74–82.
20. Barczynski, M., Randolph GW, Cernea CR, Dralle H, Dionigi G, Alesina PF, Mihai R, Finck C, Lombardi D, Hartl DM, Miyauchi A, Serpell J, Snyder S, Volpi E, Woodson G, Kraimps JL, Hisham AN; International Neural Monitoring Study Group.. 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: p. S1–14.
21. Randolph GW. The importance of pre- and postoperative laryngeal examination for thyroid surgery. *Thyroid* 2010;20:453–458.
22. Dralle H, Lorenz K. Intraoperative neuromonitoring of thyroid gland operations: surgical standards and aspects of expert assessment. *Chirurg* 2010;81:612–619.
23. Gonza'lez-Sa'ñchez C, Franch-Arcas G, Go'mez-Alonso A. Morbidity following thyroid surgery: does surgeon volume matter?. *Langenbecks Arch Surg* 2013;398:419–422.
24. Randolph GW, Dralle H, International Intraoperative Monitoring Study Group, Abdullah H, Barczynski M, Bellantone R, Brauckhoff M, Carnaille B, Cherenko S, Chiang FY, Dionigi G, Finck C, Hartl D, Kamani D, Lorenz K, Miccoli P, Mihai R, Miyauchi A, Orloff L, Perrier N, Poveda MD, Romanchishen A, Serpell J, Sitges-Serra A, Sloan T, Van Slycke S, Snyder S, Takami H, Volpi E, Woodson G. Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. *Laryngoscope* 2011;121(Suppl 1):S1–S16.
25. Dionigi G, Kim HY, Wu CW, Lavazza M, Ferrari C, Leotta A, Spampatti S, Rovera F, Raucsi S, Boni L, Chiang FY. Vagus nerve stimulation for standardized monitoring: technical notes for conventional and endoscopic thyroidectomy. *Surg Technol Int.* 2013;23:95–103.
26. Wu CW, Dionigi G, Chen HC, Chen HY, Lee KW, Lu IC, Chang PY, Hsiao PJ, Ho KY, Chiang FY. Vagal nerve stimulation without dissecting the carotid sheath during intraoperative neuromonitoring of the recurrent laryngeal nerve in thyroid surgery. *Head Neck* 2013;35:1443–1447.
27. Chiang FY, Lu IC, Tsai CJ, Hsiao PJ, Lee KW, Wu CW. Detecting and identifying nonrecurrent laryngeal nerve with the application of intraoperative neuromonitoring during thyroid and parathyroid operation. *Am J Otolaryngol* 2012;33:1–5.
28. Yamamoto S, Yamamoto Y, Kitajima O, Maeda T, Suzuki T. Reversal of neuromuscular block with sugammadex: a comparison of the corrugator supercilii and adductor pollicis muscles in a randomized dose-response study. *Acta Anaesth Scand* 2015;59: 892–901.
29. Brauckhoff M, Walls G, Brauckhoff K, Thanh PN, Thomusch O, Dralle H. Identification of the non-recurrent inferior laryngeal nerve using intraoperative neurostimulation. *Langenbecks Arch Surg* 2002;386:482–487.
30. Chiang FY, Lu IC, Chang PY, Sun H, Wang P, Lu XB, Chen HC, Chen HY, Kim HY, Dionigi G, Wu CW. Stimulating dissecting instruments during neuromonitoring of RLN in thyroid surgery. *Laryngoscope.* 2015;125:2832–2837.
31. Lu IC, Chu KS, Tsai CJ, Wu CW, Kuo WR, Chen HY, Lee KW, Chiang FY. Optimal depth of NIM EMG endotracheal tube for intraoperative Neuromonitoring of the recurrent laryngeal nerve during thyroidectomy. *World J Surg* 2008;32:1935–1939.
32. Suy K, Morias K, Cammu G, Cammu G, Hans P, van Duijnhoven WG, Heeringa M, Demeyer I. Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent. *Anesthesiology* 2007;106:283–288.
33. Pisanu A, Porceddu G, Podda M, Cois A, Uccheddu A. Systematic review with meta-analysis of studies comparing intraoperative neuromonitoring of recurrent laryngeal nerves *versus* visualization alone during thyroidectomy. *J Surg Res.* 2014;1;188:152–161.