Anesthetic Considerations of Intraoperative Neuromonitoring in Thyroidectomy

Running title: NIM Problems during Thyroidectomy

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Abstract

**Background:** Intraoperative neuromonitoring (IONM) could reduce the incidence of injury to the recurrent laryngeal nerve (RLN) during thyroidectomy. Although the dislocation of endotracheal tube surface electrodes can lead to false positive IONM results (loss of signals), the risk factors remain unclear, as does the influence of muscle relaxants. Therefore, to identify factors that can affect IONM results, we examined the frequency and risk factors of tube dislocation after cervical extension prior to surgery, the effect of sugammadex administration, and the correlation between IONM results and postoperative RLN palsy.

**Methods:** Thirty-nine patients scheduled for thyroidectomy from October 2016 to April 2017 were enrolled. All patients underwent standard IONM and pre- and postoperative laryngoscopy. Differences in patient characteristics between the tube dislocation group and the non-dislocation group, and differences in the amplitude at vagal stimulation between before and after sugammadex administration, were assessed by the Mann–Whitney test or Fisher’s exact test.

**Results:** Tube dislocation was observed in 27 patients (69%). The dislocation group (n=27) had a significantly shorter sterno-cricoid distance than the non-dislocation group (n=12) (43.88(32.2–55.91)mm vs 49.46(40.66–55.91)mm, respectively ;p=0.048). Without sugammadex, the amplitude at vagal stimulation was enough for monitoring. Nine patients had new-onset RLN palsy, but all of them were transient. The sensitivity of IONM was 100%, the predictive positive value was 60%, and the negative predictive value was 100%.

**Conclusions:** This study suggested that anesthesiologists should correct tube dislocation reliably with video laryngoscope. The dose of rocuronium 0.6 mg/kg
without sugammadex could be adequate for IONM.

**Key words:** Intraoperative nerve monitoring (IONM), thyroid surgery, sevoflurane, neuromuscular blockage, video laryngoscope
Introduction

Postoperative recurrent laryngeal nerve (RLN) palsy is a common complication after thyroidectomy and can worsen the patient’s quality of life. Intraoperative neuromonitoring (IONM) helps to ensure accurate identification of the RLN and to make sure of the nerve integrity at the end of the operation. International guidelines emphasize the benefit of IONM of the RLN. A recent meta-analysis, Yang et al. showed that the mean sensitivity and positive predictive values of IONM for RLN palsy were 66.8% (range: 36.4–93.5%) and 63.4% (range: 35–92.1%), respectively. A common reason for false positive results in regard to IONM involves the dislocation of neural integrity monitor (NIM) electromyogram (EMG) endotracheal tube surface electrodes. Kim et al. found that EMG amplitudes could change during tube dislocation in a porcine model. However, the risk factors for dislocation remain unclear, and no standard method to confirm the position of a placed tube has been established.

In recent guidelines, a small dose of a nondepolarizing muscle relaxant was recommended to limit myogenic response amplitudes in IONM for thyroidectomy. For example, rocuronium is well known as a short-acting nondepolarizing muscle relaxant, and its antagonist is sugammadex. Unfortunately, there are no direct methods to monitor the muscle contractility of vocal folds after induction, which could depend on the choice of anesthetics, and IONM time point. Since, to clear the remaining effect of muscle relaxant on IONM results, the comparison of IONM results between before and after sugammadex should be needed.

Therefore, the objectives of this study were (1) to examine the frequency of tube dislocation after cervical extension prior to surgery, (2) to identify the patient factors and tumor factors that can affect the results of tube dislocation, (3) to examine the effect
of sugammadex administration on IONM results, and (4) to check the accuracy of IONM at our hospital.

Materials and Methods

In the present study, we enrolled 39 patients with thyroid carcinoma scheduled for thyroidectomy and neck dissection from October 2016 to April 2017 at Nippon Medical School Hospital. The extent of thyroidectomy was total thyroidectomy in 15 and lobectomy in 24. Preoperative unilateral RLN palsy due to tumor invasion was seen in 2 patients. Thus, the number of RLNs at risk was 52. Informed, written consent was obtained from all patients, and the study was approved by the Institutional Committee of Nippon Medical School (approval number: 28-06-598).

No premedication was used. The vital signs of all patients were checked, including an electrocardiogram, noninvasive blood pressure measurement, and pulse oximetry. Before anesthetic induction, anesthesiologists put the graduation lines every 3 mm on the electrode of the endotracheal tube (NIM® EMG Standard Endotracheal Tube; Medtronic Japan, Tokyo, Japan). General anesthesia was induced using propofol 1–2 mg/kg, fentanyl 0.1–0.2 µg/kg, and/or remifentanil 0.1–0.3 µg/kg/min. Intubation was facilitated with rocuronium 0.6 mg/kg. For tube lubricants, normal saline was used instead of lidocaine jelly. Anesthesia was maintained with 0.7–1 minimum alveolar concentration (MAC) of sevoflurane in an air/O₂ mixture (F₂O₂ 0.4, 6 L/min), remifentanil 0.05–0.2 µg/kg/min, bolus fentanyl 1–2 µg/kg/h, and no additional dose of rocuronium. Anesthesiologists placed the tube where the middle line of the graduation lines grounded the vocal folds on both sides, using a video laryngoscope. The positions of the electrodes for IONM were observed and optimized by both anesthesiologists and
surgeons at the time of both intubation and cervical extension before surgery using a video laryngoscope (McGrath® MAC; Covidien Japan, Tokyo, Japan). We compared the tube position between the time of intubation and cervical extension. If dislocation more than 3 mm (in other words, more than 1 graduation line) was observed, the case was recorded as “dislocation positive” and the gap was corrected to the optimal position. After identifying the vagus nerve, “baseline” IONM with vagal stimulation (stimulus intensity: 3 mA) was performed (V1). Then, sugammadex 2 mg/kg was administered, and IONM was performed again 3 minutes later (V1’). IONM stimulation was also performed after tumor removal (V2). All other thyroidectomy and anesthesia procedures were performed as usual. IONM was recorded using the NIM-Response® 3.0 system (Medtronic Japan). All patients underwent laryngoscopy by an otolaryngologist and a postoperative check by an anesthesiologist on postoperative day 1.

We examined whether the tube dislocation group had any association with background factors, including patient factors, tumoral factors, and operative factors. Patient factors included age, sex, height, and body mass index, sterno-cricoid distance (distance between the cricoid cartilage and suprasternal notch on radiographic images). Tumoral factors included pathological diagnosis of thyroid tumor, tumor position, tumor size, lymph node metastasis, and preoperative RLN palsy. Operative factors included extent of thyroidectomy and lymph node dissection. We also compared the amplitude of vagal stimulation at before and after sugammadex administration. Loss of signal (LOS) was defined as V2 < 100 µV or an 80% decrease in nerve amplitude from baseline, as defined by Stopa et al.6. In addition, LOS was defined as true positive when RLN palsy was observed by laryngoscopy on postoperative day 1 and as false positive when no RLN palsy was observed7.
Statistical Analysis

All numerical data were expressed as the median (range). Differences in patient and tumor characteristics between the tube dislocation and non-dislocation groups, and differences in the amplitude at vagal stimulation between before and after sugammadex administration, were assessed by the Mann–Whitney test or Fisher’s exact test using Prism software (ver. 5.0; GraphPad Software, San Diego, CA, USA) unless otherwise specified. P values of 0.05 or less were taken to indicate statistical significance.

Results

Thirty-nine patients (19 men, 20 women) were included in the analysis. All tracheal intubations were successful on the first attempt without any difficulties.

Patient background and tube dislocation

Among these 39 patients, tube dislocation was observed in 27 (69%), 22 of whom showed caudal movement (a shortening of the distance between the tube electrodes and the carina). One of them showed a 90-degree tube rotation. In another case, tube dislocation reoccurred afterwards and the tube position was corrected during surgery. After re-correcting the tube position using the video laryngoscope, IONM was documented correctly in all cases.

The relationship between tube dislocation and various background factors is summarized in Table 1. When comparing the dislocation group (n=27) and the non-dislocation group (n=12), there were no significant differences in age, sex, height, or body mass index. In addition, no significant differences were seen in the tumoral data (number, size, and position of tumor, pathological diagnosis, or lymph node metastasis).
On the other hand, patients in the dislocation group had a significantly shorter sterno-cricoid distance than those in the non-dislocation group (43.88 (32.2–55.91) mm vs. 49.46 (40.66–55.91) mm, respectively; p=0.048).

**The effect of sugammadex administration on IONM results**

Figure 1 shows a comparison of the amplitude at vagal stimulation between before and after sugammadex administration. The time between the administration of rocuronium and sugammadex was 45 (20–72) min. A significant difference was seen between V1 and V1’ (V1: 292 (114–1283) µV, V1’: 421 (143–2012) µV; p=0.001).

![Figure 1 here](image)

**Postoperative symptoms and the accuracy of IONM**

Nine patients had new-onset unilateral vocal fold dysfunction at postoperative day 1, accounting for 17.3% of the 52 nerves at risk. There was no bilateral palsy. All of them had LOS for V2. All cases of dysfunction were transient, and no cases had permanent palsy. All the symptoms such as hoarseness and voice deterioration were disappeared within three months (1-6 months). The sensitivity of IONM was 100%, the positive predictive value was 60%, and the negative predictive value was 100 %, as shown in Table 2.

**Discussion**

In the present study, use of the endotracheal tube caused no severe adverse events, such as arytenoid subluxation or larynx edema requiring re-intubation, which suggested the safety of the NIM® EMG Endotracheal Tube.

It has been well described that the position of the endotracheal tube can be altered as a result of neck extension. In this study, EMG tube dislocation at the cervical extension
position was observed in two-thirds of the patients, and 88% of the dislocations involved caudal movement. In addition, the dislocation group tended to have a shorter sterno-cricoid distance than the non-dislocation group. Tube dislocation can be the most important factor affecting the results of IONM, so checking the tube position repeatedly if dislocation is suspected could enhance the quality of IONM, especially in patients with a short neck.

In this study, the RLN palsy was diagnosed as 1) postoperative symptoms such as hoarseness or difficulty with raising their voices and 2) postoperative vocal fold dysfunction observed by laryngoscope on postoperative day 1. RLN palsy could be occurred not only by vagal nerve injury, but also by vagal nerve extension due to surgical procedure, tube intubation or extubation. Randolph et al. showed that the transient RLN palsy would last for a short duration, such as several weeks to several months. Also, Lo CY showed that 6.6% patients developed postoperative unilateral vocal fold paralysis and that 93% of them got complete recovery during a median period of 3 months (range, 1-9 months). In the present study, nine patients had a postoperative paralysis, however symptoms disappeared within three months after operation (0-6 months). This data indicated no RLN injuries. On the other hand, Echternach M et al. showed 31.3% of patients had an injury to the vocal folds from intubation. Therefore, anesthesiologists should perform cautious intubation to minimize potential damage to the vocal folds. Previous studies have reported that video laryngoscopes enable better views of the glottis than direct laryngoscopes. Among video laryngoscopes, the McGrath® MAC allows the surgeon to confirm the position of an inserted tube. In addition, it has superior maneuverability for correcting the position of a placed tube. For IONM in thyroid surgery, where the proper adhesion of the
electrodes and vocal folds has a large impact on the results, the McGrath® MAC might therefore offer an advantage.

During IONM, all anesthetics that can cause neuromuscular blockage must be avoided\(^\text{14}\), especially muscle relaxants. This is because there are no direct methods to monitor the muscle contractility of vocal folds after induction. The international standard guideline statement for IONM recommends that succinyl choline at 2–2.5 mg/kg or a small dose of a nondepolarizing muscle relaxant may be used\(^\text{2}\). Rocuronium is well known as a nondepolarizing muscle relaxant, and its antagonist is sugammadex. Lowry et al.\(^\text{15}\) showed that the time to recovery of T1 to 25% is 45 min after administration of rocuronium 0.6 mg/kg, the recommended initial dose by FDA. Sensitivity to rocuronium and the duration of its effect are known to differ depending on the muscle sites. Meistelman, using muscle relaxation monitoring, presented data indicating that recovery from muscle relaxant action occurs earlier in the larynx than in the adductor pollicis\(^\text{16}\). In the present study, V1 recorded at around 46 minutes after rocuronium 0.6mg/kg administration were over 400μV, enough high for adequate IONM. Enough V1 amplitude for adequate IONM was gained without sugammadex, so that our data indicated the dose of rocuronium 0.6mg/kg was adequate for IONM. In addition, V1’ amplitude increased by sugammadex administration (P<0.05), suggesting the small remaining effect of rocuronium at V1 recording. The sugammadex administration could be useful to remove the remaining rocuronium effects, in case IONM would start earlier than 45 minutes after the induction, or V1 amplitude was lower than 100μV.

The influence of the anesthetic agent used for IONM in thyroid surgery has not been discussed, and no guidelines that make a specific reference to choices of anesthetic agent have been devised. For IONM in thyroidectomy, the train of four (TOF) of the
adductor pollicis was researched for assuming muscle contractility of vocal folds\textsuperscript{14}. The previous study showed 1.0 MAC of sevoflurane did not affect to TOF compared with total intravenous anesthesia (TIVA)\textsuperscript{17}. In the present study, V1 amplitudes recorded with 0.7–1.0 MAC sevoflurane were over 400\mu V, enough high for adequate IONM, suggesting that the clinical dose of sevoflurane was adequate for IONM.

In IONM, several factors can cause a false positive result, as shown in Table 3. Even though the tube position was checked after cervical extension and sugammadex administration in all cases, six nerves were falsely positive. Tube dislocation or rotation could occur during surgery. When LOS is suspected, anesthetists should compare with the potential tube dislocation and the possibility of iatrogenic vocal fold palsy. In this study, when LOS was defined after tumor removal, the rest of surgery procedures was only the skin closure in a short time. This was the reason no checks of tube location, nor no surgery procedure changes after V2 recording. The frequent direct laryngoscopic exposure can cause the temporary vocal fold palsy as mentioned above. To minimize the risk of iatrogenic hoarseness or vocal fold palsy, we refrained from repeated direct laryngoscopic exposure in this study. Within six cases of false positive of LOS, three was lobectomy and three was total thyroidectomy. If LOS were observed at low risk cases of lobectomy, anesthesiologists would consider checking the position of tube after tumor removal, just for the record.

This study did have some limitations. First, it was an observational study involving a small number of cases in a single hospital. Second, the stimulation points during IONM could have been slightly different, which could have affected the IONM results. Third, no neuromuscular monitoring was conducted; therefore, after the IONM began, we could not assess the residual effect of rocuronium 0.6 mg/kg.
In the present study, tube dislocation after neck extension was observed in 69% of the patients. After correcting the tube dislocation, no other anesthetic or tumoral factors showed any significant effects on the IONM results. This finding suggests the importance of reliable positional correction using the McGrath® MAC video laryngoscope after cervical extension.

Conflict of Interest: The authors declare no conflict of interest.
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Figure 1
|                              | Dislocation n=27 | Non-dislocation n=12 | P value |
|------------------------------|------------------|----------------------|---------|
| Dislocation (mm)            | (-12–3)          | -                    |         |
| Age                          | 47 (31–78)       | 46 (30–82)           | 0.82    |
| Height (cm)                  | 162.5 (140–193)  | 165 (138–175)        | 0.68    |
| BMI                          | 23.8 (18.1–34.8) | 22.1 (17.4–27.1)     | 0.22    |
| Sex (male : female)          | 12:15            | 7:5                  | 0.33    |
| Sterno-cricoid distance (mm) | 43.88 (32.2–55.91) | 49.46 (40.66–63.73) | 0.048*  |
| Pathological diagnosis       |                  |                      |         |
| Papillary carcinoma          | 26               | 10                   | 0.22    |
| Medullary carcinoma          | 1                | 1                    | 0.53    |
| Undifferentiated carcinoma   | 0                | 1                    | 0.31    |
| Multiple tumors              | 7                | 0                    | 0.078   |
| Position of tumor            |                  |                      |         |
| Upper                        | 14               | 6                    | 1       |
| Middle                       | 13               | 8                    | 0.32    |
| Lower                        | 12               | 8                    | 0.30    |
| Other                        | 2                | 2                    | 0.57    |
| Maximum tumor size (mm)      | 15 (0.5–65)      | 18 (5–44)            | 0.72    |
| Lymph node metastasis        | 18               | 8                    | 0.65    |
| Preoperative RLN palsy       | 2                | 0                    | 0.86    |
| Operative procedure          |                  |                      |         |
| Total thyroidectomy : lobectomy | 13:14            | 2:10                 | 0.13    |
| Lymph node dissection        |                  |                      |         |
| Central                      | 16               | 8                    | 0.47    |
| Lateral                      | 9                | 4                    | 0.65    |
| Bilateral                    | 2                | 0                    | 0.93    |

Values are expressed as N or median (range).

BMI, body mass index; RLN, recurrent laryngeal nerve

*p<0.05
Table 2. The association between presence of RLN palsy and LOS in IONM.

|       | RLN palsy | No RLN palsy | Total |
|-------|-----------|--------------|-------|
| LOS   | 9         | 6            | 15    |
| No LOS| 0         | 37           | 37    |
| Total | 9         | 43           | 52    |

Values are expressed as N.

IONM, Intraoperative neuromonitoring; RLN, recurrent laryngeal nerve; LOS, loss of signals
Table 3. The causes of false positivity at IONM.

| Causes                                      |
|---------------------------------------------|
| Improper position of NIM tube               |
| Protracted effect of muscle relaxant        |
| Lubricating gel on NIM tube                 |
| Equipment malfunction                        |
| Improper intensity of stimulation           |
| Anatomic variations of RLN                  |

IONM, Intraoperative neuromonitoring; NIM, neural integrity monitor; RLN, recurrent laryngeal nerve