THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2021.26675
Med Bull Sisli Etfal Hosp 2021;55(3):273–285

Review

Recent Developments of Intraoperative Neuromonitoring in Thyroidectomy

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Abstract

At present, intraoperative neuromonitorization (IONM) with surface electrode-based endotracheal tube (ETT) is a standard method in thyroidectomy and can be performed either intermittently IONM (I-IONM) or continuously IONM (C-IONM). Despite the valuable contribution of I-IONM to the thyroidectomy, it still has limitations regarding the recording electrodes and stimulation probe. New approaches for overcoming the limitations of I-IONM and developing the method are taking attention. Most of the technical issues of IONM with surface electrode-based ETT are related with inadequate contact of electrodes to the vocal cords. Nowadays, efficiency of various recording electrodes is under investigation. Recording electrodes such as needle electrodes applied to thyroarytenoid or posterior cricoarytenoid muscle (PCA), surface electrodes applied to the PCA, and needle or adhesive electrodes applied to the tracheal cartilage or skin, can make safe recordings similar to the ETT electrodes. Despite their invasiveness, needle electrodes record higher electromyography (EMG) amplitudes than tube electrodes do. Adhesive surface electrodes make safe EMG recordings, although amplitudes of these electrodes are usually lower than those of the tube electrodes. These different types of electrodes are less affected by tracheal manipulations and amplitude changes are lower compared to the tube electrodes.

During C-IONM, an additional stimulation probe is applied to the vagus nerve after dissecting the nerve circumferentially. Recently, without applying a probe, a new continuous monitorization method called laryngeal adductor reflex CIONM (LAR-CIONM) using sensorial, central, and motor components of LAR arch which is an automatic, primitive brainstem reflex protecting the tracheo-esophageal tree from foreign body aspiration, has been implemented. Afferent track of LAR communicates laryngeal mucosa to the brainstem by internal branch of the superior laryngeal nerve and efferent track reaches larynx through recurrent laryngeal nerve. Total outcome of LAR activation is the closure of laryngeal entry by bilateral vocal cord adduction. In LAR-CIONM, a stimulus is given by an electrode from one side of surface electrode-based ETT and amplitude response of the LAR at the vocal cord is followed on the operation side. Recently, it has been reported that real-time EMG response can be obtained with stimulation probe cables applied to dissectors or energy devices during the dissection through I-IONM.

Keywords: Electromyography; neuromonitorization; recurrent laryngeal nerve; superior laryngeal nerve.

Please cite this article as: Aygun N, Kostek M, Isgor A, Uludag M. Recent Developments of Intraoperative Neuromonitoring in Thyroidectomy. Med Bull Sisli Etfal Hosp 2021;55(3):273–285.

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Submitted Date: August 10, 2021 **Accepted Date:** August 16, 2021 **Available Online Date:** September 24, 2021

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Introduction

Thyroidectomy is the most common endocrine surgical intervention and laryngeal nerve injuries are still among main complications. Intraoperative neuromonitorization (IONM) is a complementary, dynamic method on the basis of functional assessment of nerves in thyroidectomy in addition to the visual identification which is the gold standard for nerve protection.[1] IONM is a method improving the standards of thyroidectomy in many ways.[2]

Use of IONM in thyroidectomy is increasing steadily. Nowadays, IONM with surface electrode-based endotracheal tube (ETT) is applied as a standard technique. IONM is mostly applied as intermittent IONM (I-IONM) (Figure 1) and less frequently as continuous IONM (C-IONM) (Figure 2). The standards of I-IONM have been defined by the International Intraoperative Monitoring Study Group. For optimal IONM, pre-operative and post-operative laryngoscopy, obtaining intraoperative electromyographic responses through vagus (V1) and recurrent laryngeal nerve (RLN) stimulations (R1) before resection and vagus (V2) and RLN (R2) stimulations after resection are recommended.[1]

I-IONM is an efficient tool for detecting the localization of RLN, whether a loss of signal (LOS) occurred or not and also detecting the type of LOS (LOS 1, LOS 2), and staged thyroidectomy in the presence of LOS. However, I-IONM does not give any information about possible injuries during dissection between two stimulations. On the other hand, I-IONM can detect injury after it occurs. C-IONM is a real-time monitorization through repeated stimulations applied with a probe (probe type; open, semi-closed, or closed) implemented after circumferential dissection of vagus nerve, which can detect and prevent progressive nerve injury in traction trauma.[2]

Both techniques have several limitations. Experimental and clinical studies continue to overcome these limitations and/or to improve IONM. In this study, we aimed to evaluate new approaches in the literature and studies related to IONM.

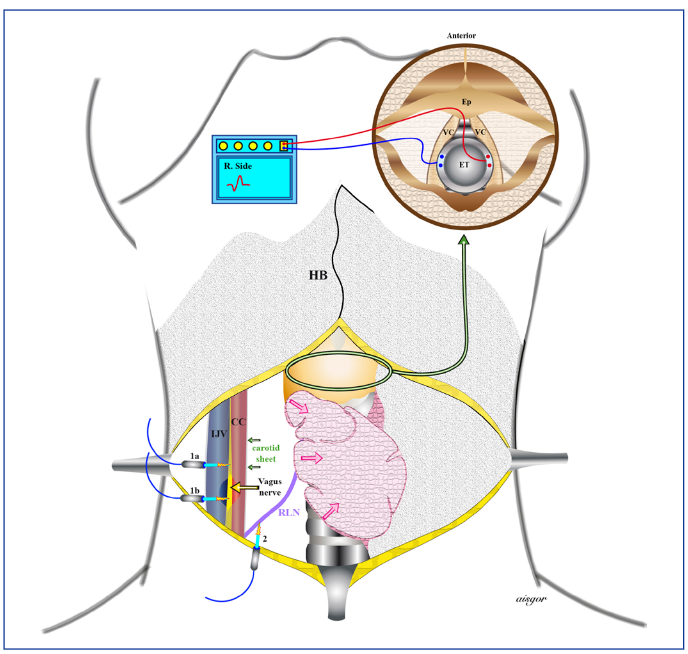

Figure 1. Intermittent intraoperative neuromonitoring using surface electrode-based endotracheal tube, R side: Right side, ET: Endotracheal tube, VC: Vocal cord, Ep: Epiglottis, HB: Hyoid bone, IJV: Internal jugular vein, CC: Common carotid artery, RLN: Recurrent laryngeal nerve, stimulation of vagus nerve over the carotid sheath using stimulating probe (1a), stimulation of vagus nerve using stimulating probe after carotid sheath is opened (1b), stimulation of RLN using stimulating probe[2].

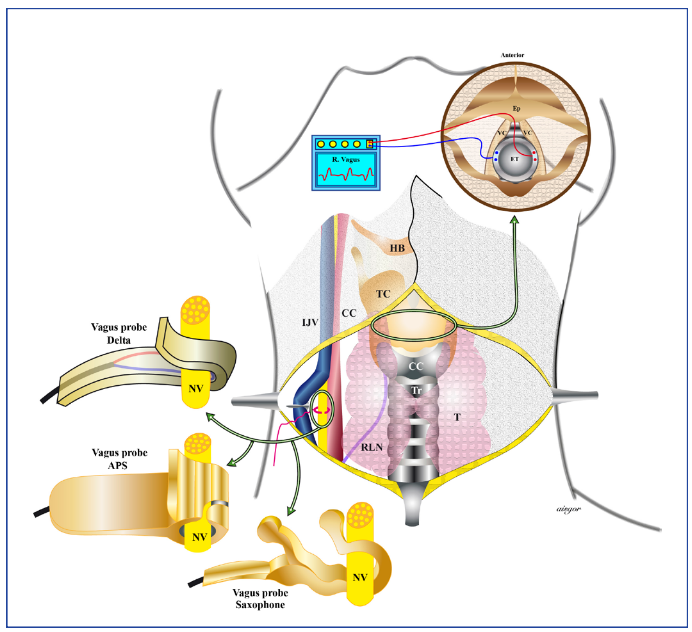

Figure 2. Continuous intraoperative neuromonitoring using surface electrode-based endotracheal tube, R side: Right side, ET: Endotracheal tube, VC: Vocal cord, Ep: Epiglottis, HB: Hyoid bone, IJV: Internal jugular vein, CC: Common carotid artery, RLN: Recurrent laryngeal nerve, T: Thyroid, Tr: Trachea, CC: Cricoid cartilage. Continuous vagus stimulating probes that are used in daily practice are manufactured by three different companies: Delta electrode (Inomed Medizintechnik GmbH, Emmendingen/Germany), Saxophone electrode (Dr. Langer Medical GmbH, Waldkirch/Germany), APS™ (Automatic Periodic Stimulation™) electrode(Medtronic, Jacksonville, Florida).

New Approaches to the Recording Electrodes In IONM

On top of studies regarding the IONM, new investigations for recording electrodes take attention. To decrease technical problems in IONM, interdisciplinary communication and experiences of both surgical team and anesthesiology team are crucial. During IONM through ETT with surface electrodes, 93% of technical problems are related with inappropriate contact of tube electrodes to the vocal cords.[3]

According to the position of ETT electrode compared to its optimal position, mean electromyography (EMG) amplitudes decreased with vertical displacement of the electrode by 43% at 1 cm inferior, 76% at 2 cm inferior, 68% at 1 cm superior, 80% at 2 cm superior to the baseline, and 22% with 45° clockwise rotation, 40% with 45 degree counter clockwise rotation, 36% with 90 degree clockwise rotation, 47% with 90 degree counter clockwise rotation, and 18% with 180 degree rotation. There was no significant change in mean EMG latency values by tube rotation or localization changes in vertical position.[4]

During thyroidectomy, a decrease of amplitude or false-positive LOS may occur easily related to the inadequate contact between electrodes and vocal cords after change of ETT position due to the traction of the trachea. To adjust false IONM results, the anesthesiologist may be required for the verification and reposition of the intraoperative electrodes.[5]

Intubation with surface electrode-based ETT may not be performed due to the severe compression of trachea in large goiters. ETT with surface electrodes may not be applied to the patients with tracheostomy. Changing a standard ETT with an electrode-based ETT might be difficult in patients in unexpected requirement of IONM during the surgery.[6]

Due to these limitations, recording electrodes other than ETTs are under investigation for IONM.

Thyroid Cartilage Electrodes

Subperichondrial Needle Electrodes

Chiang *et al*. placed single-(Fig. 3a) or double-needle electrodes (Figure 3b) subchondrially to the middle portion of each lateral lamina of thyroid cartilage in a 10–15 degree angle oblique to the thyrohyoid muscle's anterior edge. Cables of electrodes were fixed with sutures to the pre-laryngeal tissue.[6,7]

Lee *et al*. reported that recording of stable EMG waves was possible in patients with either superficial (<5mm) and deep (>5mm) application (Fig. 3b) of subpericondrial dual needle electrodes and no significant complication occurred. In addition, authors detected lower amplitude values with vagus and RLN stimulation when the needle electrode was applied superficially.[8]

Chiang *et al*. compared EMG results of thyroid cartilage electrodes with EMG results of ETT electrodes in 110 patients and 205 nerves. Although both electrodes safely recorded EMG signals, EMG amplitudes in V1 and R1 stimulations were 2–2.5 times higher in thyroid cartilage electrodes than ETT electrodes. While V1 amplitude should be more than 500 μV in first installation for an ideal IONM, V1

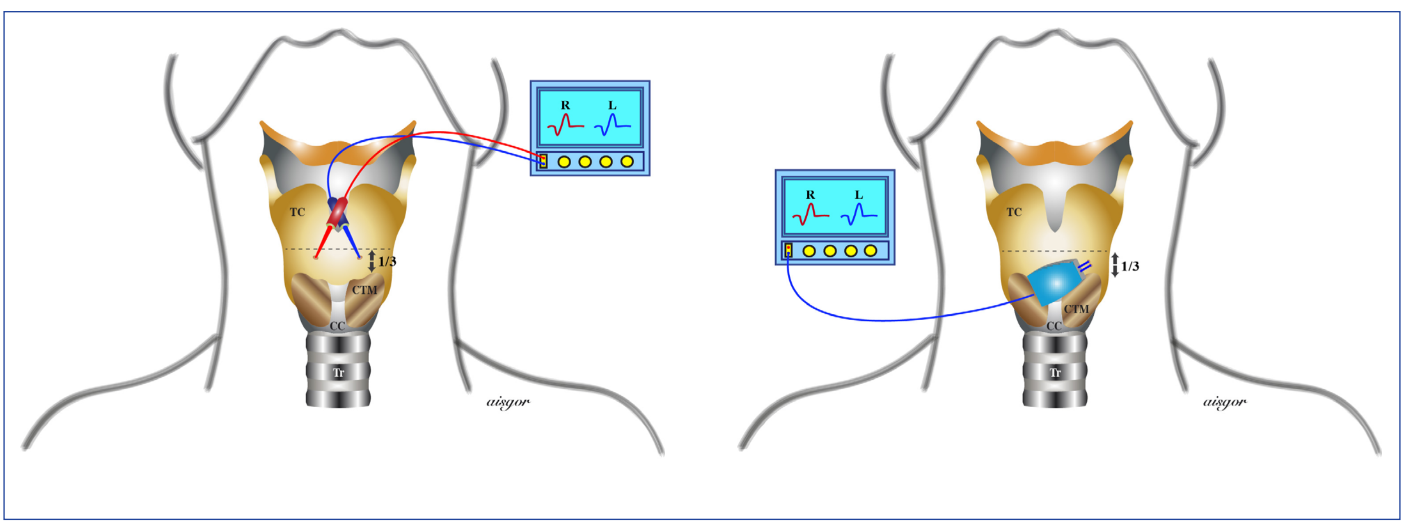

Figure 3. (a) Intraoperative neuromonitoring using singletip needle electrode which is applied subperichondrially to the thyroid cartilage, (b) Intraoperative neuromonitoring using doubletip needle electrode which is applied subperichondrially to the thyroid cartilage, TC: Thyroid cartilage, R: Right, L: Left, CTM: Cricothyroid muscle, CC: Cricoid muscle, Tr: Trachea.

amplitudes were lower than 500 µV in 36% of nerves with tube electrodes and <1% with thyroid cartilage electrodes. Both electrodes detected EMG changes appropriately in seven nerves with partial signal decrease due to traction and in two nerves with LOS. In addition, by tube electrodes, false-positive LOS was detected in three nerves due to the changed tube position after surgical manipulation, however, no false-positive LOS was detected by thyroid cartilage electrodes. Data of signal changes between first and final stimulation (V2/V1) were evaluated in 196 nerves without RLN signal reduction. Nerve numbers without signal reduction (defined as V2/V1: 80–120%) from thyroid cartilage and tube electrodes were 80% and 50%, with signal increase (V2/V1: >120%) were 17% and 26%, and with signal reduction (defined as V2/V1 <80%) were 1% and 24%, respectively. In addition, in 20 (10.2%) nerves, >50% decrease of amplitude was detected by ETT electrodes, and there was no decrease of amplitude by thyroid cartilage electrodes in any of these nerves. Authors concluded that lower false EMG results and more stable EMG signals were recorded by thyroid cartilage electrodes.[6]

Due to the fact that these electrodes were placed in surgical site, any malposition can be assessed by surgeon and position of the probe can be adjusted if needed. Invasiveness is considered as the main disadvantage, although investigators reported no complication, and also easy application in a short time and no easy dislodgement. The electrodes do not fully penetrate the thyroid cartilage and are placed subperichondrially.

Transcartilage Surface Electrodes

Wu *et al*. evaluated transcartilage surface electrodes in a swine model applying adhesive gelled electrodes to the right and left lamina of tracheal cartilage (TC). After stimulating vagus and RLN, recorded EMG amplitudes were higher in tube electrodes and latency was similar. Acquired amplitudes from TC electrodes were approximately 70% of ETT. In an experimental model, subsequent to changing location of trachea 1 cm superiorly, lower variation of EMG signals in TC electrodes was observed compared to ETT electrodes. Following traction stress and recovery on RLN, appropriate and similar EMG changes were observed with both electrodes. Investigators postulated that these new adhesive electrodes may be used as an alternative to the ETT electrodes in IONM. In addition, adhesive electrodes applied in this experimental model were pediatric electrocardiography electrodes for chest skin. Authors declared that more studies were needed for design of electrodes by optimization of shape and size, for stability of adhesive electrodes and to improve sensitivity before clinical application.[9]

In two clinical studies, IONM data from TC surface electrodes were compared with data from tube electrodes. In both studies, one Dragonfly type bipolar surface electrode (Neurovision Medical Products, Ventura, CA) was divided into two pieces, each part was sutured to perichondrium of right and left thyroid lamina and anterior laryngeal monitorization was applied using these electrodes as anterior laryngeal electrodes (Fig. 4).

Liddy *et al*. evaluated 20 neck sides in 15 patients using these electrodes that were defined as anterior laryngeal electrodes by the authors. After vagus and RLN stimulation, recorded EMG amplitudes by anterior laryngeal electrodes were approximately 80% of the amplitudes obtained through ETT electrodes and this reduction was statistically significant. Investigators mentioned that these results seemed like signal attenuation while passing through thyroid cartilage to reach anterior laryngeal electrodes. Moreover, acquiring lower amplitudes by anterior laryngeal electrodes are not a risk factor for false-negative results of nerve stimulation. During stimulation of external branch of the superior laryngeal nerve (EBSLN), acquired amplitudes by anterior laryngeal electrodes were more than 800% of amplitudes recorded by ETT electrodes. These results related with short distance between electrodes and cricothyroid muscle that is the target muscle of EBSLN and recording amplitude of contraction of this muscle.[10]

However, in a study by Van Slycke *et al*., 43 neck sides in 25 patients were evaluated and they recorded higher amplitudes by transcartilage electrodes compared to ETT electrodes after stimulation of the left vagus nerve and both RLNs and EBSLNs on each side except right vagus nerve. In that study, investigators explained the reason of the

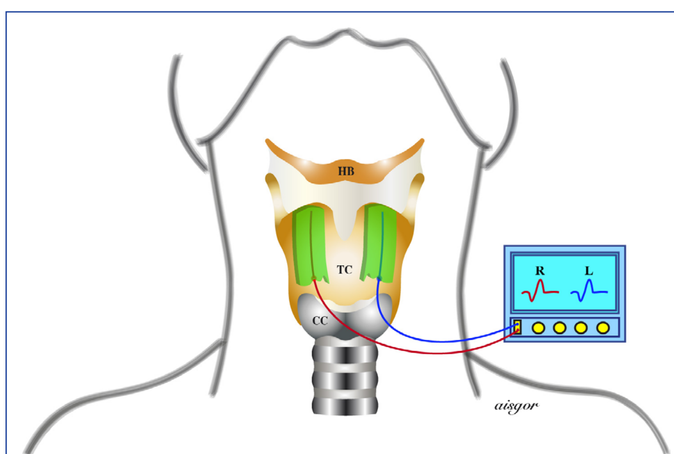

Figure 4. Intraoperative neuromonitoring with transcartilage adhesive electrode (HB: Hyoid bone, TC: Thyroid cartilage, R: Right, L: Left, CC: Cricoid cartilage).

difference with recording higher amplitudes because of close distance of electrodes to the thyroarytenoid muscle and absence of foreign materials such as blood, air, or mucus between vocal cords and electrodes.[11]

Electrodes in both studies were not designed for anterior laryngeal area. Furthermore, electrodes were attached with a suture invasively. To apply transcartilage electrodes, wider skin incisions may be needed to expose the cartilage. The electrodes in the anterior laryngeal area were located in the surgical site. Thus, the position and dislocation of these electrodes should be controlled by surgeons. In addition, after developing non-invasive adhesive electrodes, this method appears as an alternative applicable technique.

Transcutaneous Surface Electrodes

Wu *et al*. evaluated data from adhesive cutaneous electrodes and ETT electrodes in a swine model with a hypothesis that electrophysiological response of thyroarytenoid muscle might be recorded with adhesive cutaneous electrodes applied to the skin similar to the thyroid cartilage needle or surface electrodes. Swine was intubated with surface electrode-based ETT, at the same time, couple of adhesive gel electrode (Neotrode II®, ConMed Corporation, Utica, NY) were attached to the skin at the upper level of the right and left lamina of thyroid cartilage, both skin and ETT electrodes were connected to the monitoring interface and recorded simultaneously. Amplitudes from vagus and RLN stimulations were lower and around 25–30% of amplitudes from ETT electrodes. Latencies were similar in recording from two electrodes.[12] Although experimental tracheal shift by hanging trachea significantly affected the EMG changes with ETT electrodes in C-IONM, there was no significant effect on EMG signals recorded through transcutaneous electrodes.[12]

During experimental traction trauma to the RLN through hanging the nerve with vascular loop, progressive decrease of C-IONM EMG amplitudes and after the termination of traction, increase of amplitudes were recorded as same type signal changes in both transcutaneous and ETT electrodes.[12]

These electrodes are cheaper than tube and needle electrodes. Cutaneously applied electrodes may be dislodged by skin traction. To overcome this problem, electrodes were placed as proximally as possible and were wrapped with a transparent membrane as Tegaderm (3M, Maplewood, Minnesota) or OPSITE film(Smith and Nephew, Watford, UK).[12]

Suitability of transcutaneous electrodes in detection of neurophysiologic events is demonstrated, but relatively lower mean amplitude values during IONM may still be inadequate for early detection of traction stress to prevent RLN injury. Wu *et al*. claimed that there is a possibility in future for conversion of these electrodes to electronic electrodes that may increase EMG amplitudes.[12]

Transcutaneous skin electrodes were also applied to the human subjects (Figure 5). Data of 39 nerves acquired from endotracheal electrodes and skin electrodes were compared in a study with human subjects. Absence of nerve injury was confirmed by post-operative laryngoscopy. In every stage of IONM, amplitude values were lower with skin electrodes but there was no difference between latencies. Mean V2 amplitudes acquired from ETT electrodes were approximately 4 times higher than amplitudes acquired from adhesive skin electrodes. Although LOS (<100 µV) occurred in 4 (10.3%) nerves with ETT electrodes, acceptable (>100 µV) biphasic EMG waves were recorded by adhesive skin electrodes in all of these nerves. By skin electrodes, EMG amplitude <100 µV was recorded on 10 (25.6%) nerves at V1 signal and on 3 (7.7%) nerves at V2 signal. These EMG waves were biphasic type that is typical for RLN integrity. In addition, <100 µV EMG amplitude was not recorded at R1, R2p, and R2d stimulations of any nerves. Adhesive skin electrodes can prevent false-positive LOS, especially recorded by ETT electrodes. However, adhesive skin electrodes may not be applicable in giant goiters or in cases with a need for additional flap dissection superior to the thyroid cartilage. Even though low amplitude is the major limitation of this technique, it has been claimed that this method can be considered as an alternative procedure.[13]

IONM With Posterior Cricoarytenoid Muscle (PCA) Surface Electrodes

PCA is both adductor and abductor muscle of vocal cords and its motor innervation is supplied by RLN. Surface

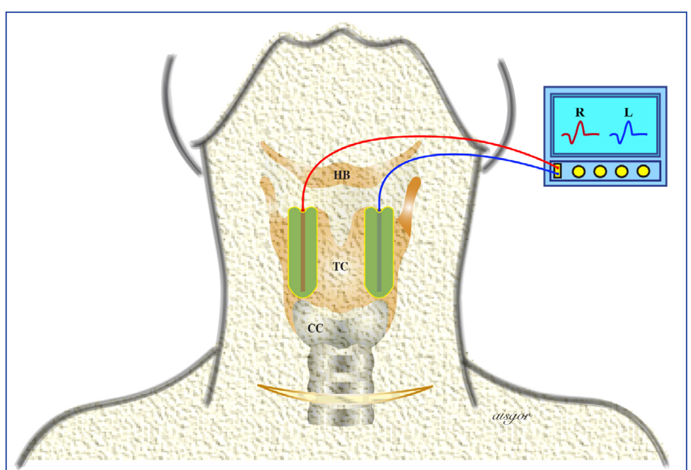

Figure 5. Intraoperative neuromonitoring with transcutaneous adhesive electrodes (HB: Hyoid bone, TC: Thyroid cartilage, R: Right, L: Left, CC: Cricoid cartilage).

electrode-based ETT records EMG data from main adductor muscle or adductor muscles of vocal cord and is not reflects the function of PCA which is the only abductor muscle of the larynx.[1]

PCA monitorization in addition to IONM with surface electrode-based ETT gives information for reaction of both adductor and abductor muscles of larynx and ensures complete evaluation of glottic function. When the importance of laryngeal abduction to keep glottic airway open is considered, PCA monitorization has a potential for being the safest method to estimate the width of post-operative airway.[14]

IONM with PCA surface electrodes is not a new method. This technique is first applied by Rea before surface electrode-based ETT (Figure 6).[15]

After that, PCA IONM with surface electrode using a spoon shape designed laryngeal surface electrode (RLN systems, Inc., Jefferson City, MO) was applied by the team of same

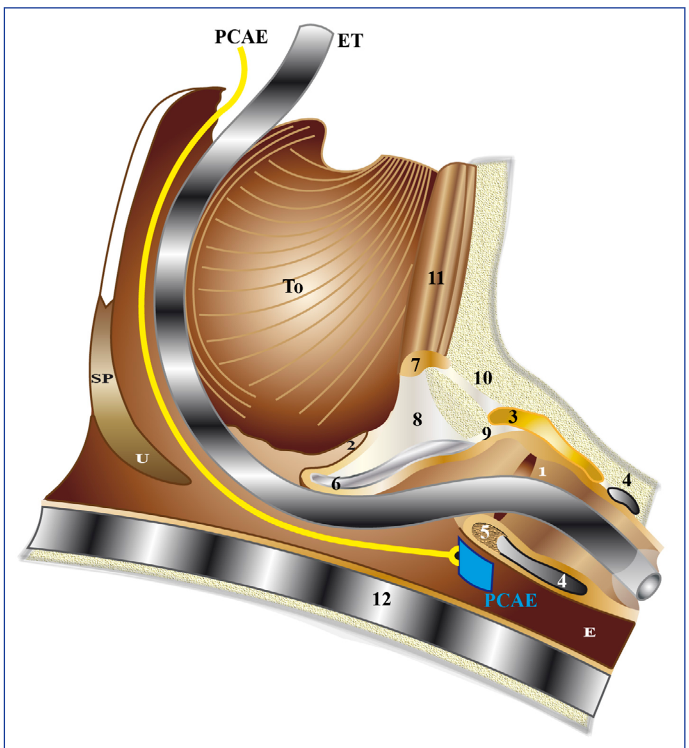

Figure 6. Intraoperative neuromonitoring with posterior cricoarytenoid muscle surface electrodes (ET: Endotracheal tube, E: Esophagus, PCAE: Posterior cricoarytenoid electrode, SP: Soft palate, U: Uvula, To: Tongue, (1) vocal cord, (2) foramen caecum, (3) thyroid cartilage, (4) cricoid cartilage, (5) posterior cricoarytenoid muscle, (6) epiglottis, (7) hyoid bone, (8) quadrangular membrane, (9) thyroepiglottic membrane, (10) thyrohyoid membrane, (11) geniohyoid muscle, (12) vertebra).

investigator. In this technique, patients are under anesthesia, are intubated with an ETT and suitable position is given before laryngeal surface electrode is placed. Larynx and ETT are elevated by a laryngoscope. Spoon-shaped laryngeal surface electrode is pushed forward along the posterior wall of the pharynx, until the electrode disappears behind the arytenoids. Then, larynx is placed over the electrode and ETT and laryngeal surface electrodes are fixed.[16,17]

In addition, quantitative analysis of EMG data was missing in these studies. Lately, similar EMG data with PCA surface electrodes and surface electrode-based ETT were found in studies with canine models.[14] In a recent study, a special bipolar surface electrode was fixed on a nasogastric tube for PCA monitorization and placed adjacent to the PCA and posterior to cricoid cartilage at hypopharynx.[18]

EMGs acquired from vagus and RLN by surface electrode-based ETT and PCA electrode were compared in a study with human subjects. Mean EMG amplitude after vagus stimulation was726±109 μV from ipsilateral vocal cord and 329±34 μV from PCA as well as mean EMG amplitude after RLN stimulation was1060±140 μV from ipsilateral vocal cord and 564±116 μV from PCA. There was no difference between PCA and vocal cord latencies. Although amplitudes from PCA EMG were approximately half of the amplitudes from vocal cords, reliable EMG waves were acquired from PCA surface electrodes. This method can be used as an alternative IONM technique. Because of its ability to give information about adductor function of vocal cord, when applied together with IONM by ETT, provides additional information about abductor function of RLN to the surface electrode based IONM.[18]

After widespread use of ETT-based IONM, this technique did not become a popular method. Although IONM with PCA surface electrode is a non-invasive method, need for an additional device other than ETT is one of the important factors that prevent this technique becoming popular.

Laryngeal Needle Electrodes

Laryngeal needle electrodes have been used before IONM with surface electrode-based ETT.[19,20] IONM was applied through needle electrodesplaced endoscopically or through cricothyroid membrane. In addition, recently, the presence of studies of IONM techniques with needle electrodes still attracts attention. IONM was applied by a single or double tip bipolar needle electrode through cricothyroid membrane or double tip bipolar needle electrode on each vocal cord separately (Figure 7). These electrodes have been reported to be safe in studies.[21-23]

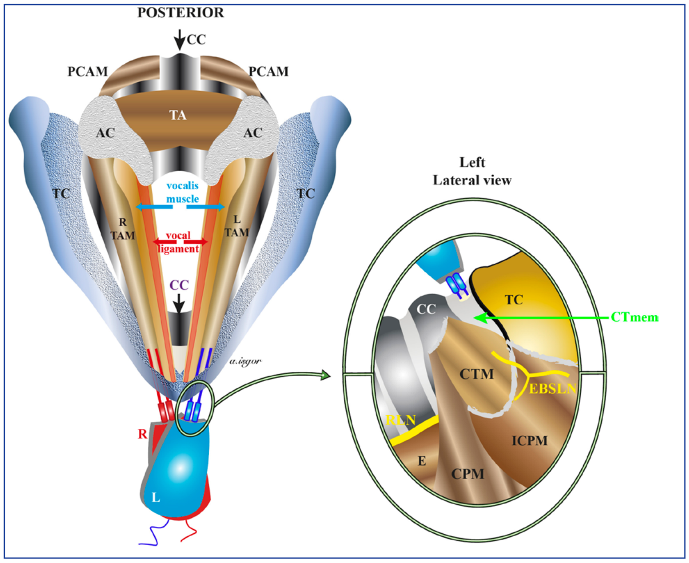

Figure 7. Intraoperative neuromonitoring by applying doubletip needle electrode to both vocal cords through cricoid membrane (TC: Thyroid cartilage, CC: Cricoid cartilage, AC: Arytenoid cartilage, TA: Transarytenoid muscle, PCAM: Posterior cricoarytenoid muscle, R TAM: Right thyroarytenoid muscle, L TAM: Left thyroarytenoid muscle, R: Needle electrode which is applied to right vocal cord, L: Needle electrode which is applied to left vocal cord, EBSLN: External branch of the superior laryngeal nerve, PCAM: Posterior cricoarytenoid muscle, CT mem: Cricothyroid membrane, CTM: Cricothyroid muscle, CPM: Cricopharyngeal muscle, IPCM: Inferior pharyngeal constrictor muscle, RLN: Recurrent laryngeal nerve, E: Esophagus.

Haerle *et al*. applied bipolar needle electrodes to both thyroarytenoid muscle and PCA by laryngoscope and reported that IONM with PCA electrode is straightforward, efficacious, and as reliable as vocalis muscle (thyroarytenoid muscle) IONM, especially in complex laryngeal anatomy.[24]

PCA EMG can be applied during thyroidectomy by bipolar double tip needle electrode attached to the PCA through the inferior fibers of cricopharyngeal muscle (Figure 8).[25] In case of an intraoperative technical problem that could not be solved with ETT-based IONM, an experienced surgeon can continue with one of the needle electrode methods.

Typically, EMG amplitudes were higher in needle electrodes than ETT electrodes. However, needle electrodes have no real advantage over surface electrodes. Measurements with ETT surface electrodes are well correlated with measurements of needle electrodes. Application of needle electrodes is invasive. Therefore, use of needle electrodes increases the possibility of vocal cord or larynx hematoma, laceration of vocal cord, or infection. Furthermore,

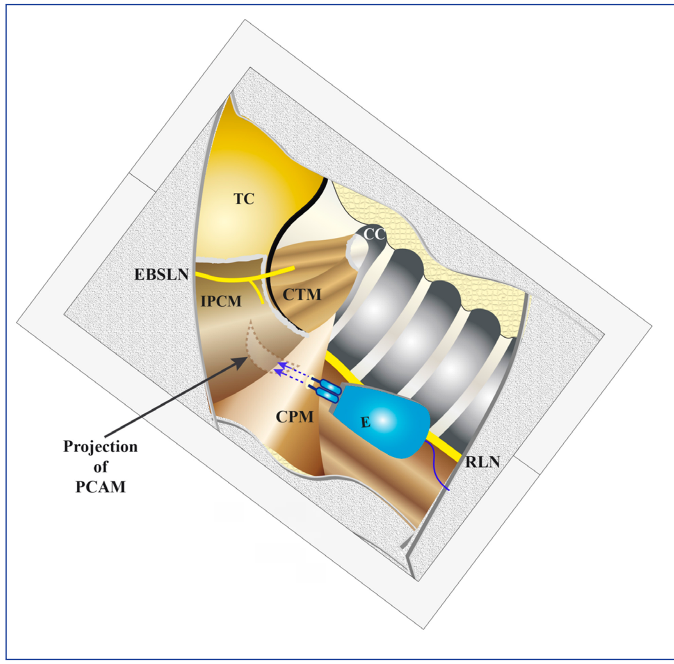

Figure 8. Intraoperative neuromonitoring by applying needle electrode to posterior cricoarytenoid muscle (EBSLN: External branch of the superior laryngeal nerve, PCAM: Posterior cricoarytenoid muscle, IPCM: Inferior pharyngeal constrictor muscle, TC: Thyroid cartilage, CC: Cricoid cartilage, CTM: Cricothyroid muscle, CPM: Cricopharyngeal muscle, RLN: Recurrent laryngeal nerve, E: Doubletip needle electrode).

needle electrode can puncture the cuff of intubation tube and reintubation may be needed. Needle may brake and remain inside of laryngeal tissue. Needle may dislocate accidentally during operation.[1]

Continuous Intraoperative Nerve Monitoring With Laryngeal Adductor Reflex (LAR)

LAR

LAR is an unintentional, primitive brainstem reflex which protects tracheobronchial tree from aspiration of foreign bodies and results with vocal cord adduction after mechanical or chemical stimulation of laryngeal mucosa. Furthermore, LAR is named as laryngeal closure reflex. LAR is a polysynaptic reflex. The stimulation on supraglottic mucosa reaches to the nucleus tractus solitarius (NTS) on brainstem through internal branches of the superior laryngeal nerve (SLNI) and vagus that is the afferent pathway of LAR. Stimulation reaching the NTS is projected to the motor neurons of nucleus ambiguus through at least two synapses. Synapses were thought as first one from ipsilateral NTS to ipsilateral nucleus ambiguus and second one to ipsilateral and contralateral nucleus ambiguus possibly through the synapses inside of reticular formation.[26,27]

Efferent pathway of LAR reaches to the larynx through vagus and RLN. Overall consequence of LAR activation is the closure of laryngeal entrance by bilateral vocal cord adduction to protect tracheobronchial tree (Figure 9).[28]LAR has two bilateral components: Early (R1) and late (R2) which are more variable. In studies, the electrical stimulation of SLNI was demonstrated to induce various recordable responses of adductor muscles of larynx. In awake humans, early ipsilateral R1 (iR1) and late bilateral R2 (iR2 and cR2) thyroarytenoid muscle response were recorded after LAR activation.[29]

Bilateral R1 (iR1 and cR1) responses were recorded in awake human subjects in a recent study.[30] Contralateral R1 (cR1) response was recorded in cats under anesthesia,

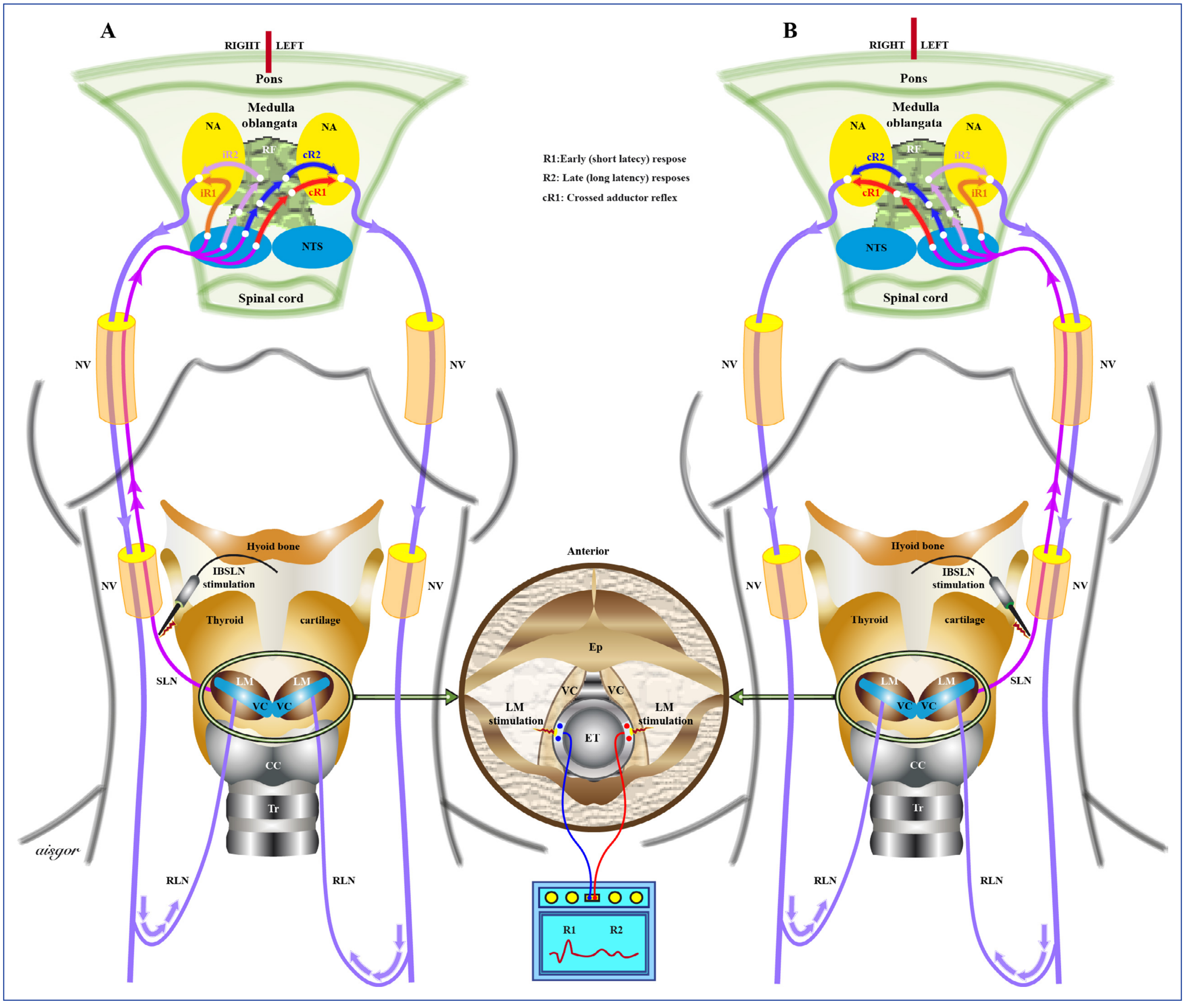

Figure 9. Continuous nerve monitoring using laryngeal adductor reflex (LAR-CIONM) (A: Bilateral LAR response after stimulation of right vocal cord mucosa, B: Bilateral LAR response after stimulation of left vocal cord mucosa) (The stable cR1 response is evaluated in LAR-C-IONM) (NA: Nucleus ambiguus, RF: reticular formation, NTS: Nucleus tractus solitarius, iR1: Early ipsilateral reflex response, iR2: Late ipsilateral reflex response, cR1: Early contralateral reflex response, cR2: Late contralateral reflex response, NV: Vagus nerve, SLN: Superior laryngeal nerve, IBSLN: Internal branch of the superior laryngeal nerve, RLN: Recurrent laryngeal nerve, VC: Vocal cord, LM: Laryngeal mucosa, CC: Cricoid cartilage, Tr: Trachea, Ep: Epiglottis, ET: Endotracheal tube).

awake human subjects, and human subjects under low-dose general anesthesia. Under general anesthesia, bilateral R1 (iR1 and cR1) responses were observed, however under anesthesia with high-dose inhalation anesthetic agents, cR1 response disappeared. As a result, responses were suppressed due to the anesthetic agent doses.[26] In the previous studies, latencies were 10–18 ms for early ipsilateral R1 response and 50–80 ms for late bilateral R2 response.[29-31]

Sasaki *et al*. reported that latency of cR1 response was 4ms longer than iR1 and suggested various brainstem circuit models for iR1 and cR1 responses. Nerve conduction rate was 5 cm/ms and each of the synaptic delay was 1.5 ms. Four milliseconds extra time for cR1 when compared to iR1 supported that there were 2 or 3 more interneuronal synapses at reticular formation.[26]

Lately, Sinclair *et al*. stimulated vocal cord mucosa by ETT-based electrodes in patients who underwent thyroid or cervical vertebra surgery under total intravenous anesthesia and recorded cR1 and cR2 responses of LAR with contralateral electrodes on ETT. LAR cR1 response was detected in all patients and it has been reported that it can be recorded without weakening for several hours. LAR cR2 response was detected 66.7% at the beginning of surgery and 23.8% at the end of the surgery. Latencies for cR1 (mean±standard deviation) were detected 22.5±2.5 ms at the left side and 23.4±3.3 ms at the right side. Amplitudes for cR1 (mean±standard deviation) were detected as 237.9±153.9 µV at the left side and 265.0±226.5 µV at the right side. Latencies for cR2 (mean±standard deviation) were detected as 59.8±4.9 ms at the left side and 61.8±7.9 ms at the right side. Intraoperative cR1 amplitude decreases reversibly correlated with the surgical maneuvers that stretch or compress RLN or SLNI. Inhalation anesthetic agents eliminate cR2 response at mean alveolar concentration >0.5 and minimalize cR1 response. Topical laryngeal anesthesia significantly decreases amplitude response of LAR. Authors reported that C-IONM is possible by stimulating and recording cR1 response of LAR using surface electrode-based ETT. This method is a C-IONM technique using sensorial, central, and motor components of LAR arch that is a vagal reflex.[28]

This technique has been started to use as a continuous LAR-C-IONM method in thyroid surgery clinically.[32,33] Since the vagus nerve can be monitorized continuously by this method, LAR-C-IONM canal so be applied in vagal schwannoma, cerebellar-pontine angle, and brainstem surgeries.[34–38] In LAR-C-IONM technique, integrity of both sensorial and motor pathways can be evaluated without applying a vagus probe.

Method

The technique that is applied by Sinclair *et al*. will be described. Due to elimination or reduction of LAR response by inhalation anesthesia, total intravenous anesthesia is applied in these patients until LAR-C-IONM is completed. During LAR-C-IONM, inhalation anesthetics or topical agents should not be used. After LAR-C-IONM is terminated, inhalation anesthesia can be used to quicken extubation.

After low-dose muscle relaxants were applied, patients were intubated through surface electrode-based ETT (Nerve Integrity Monitor [NIM] TriVantage™, Medtronics Xomed Inc.; Jacksonville, FL, U.S.A.) and electrodes were placed at the level of the vocal cords. Two electrodes on both the right and left sides of the ETT contacted directly to the vocal cords. Axon Sentinel 4 EP Analyzer device was used (Axon Sentinel 4 EP Analyzer machine Axon Systems Inc.; Hauppauge, NY, U.S.A.) for LAR-C-IONM stimulation and recording. NIM-3 device (NIM-Response 3.0 machine) (Medtronic Xomed, Inc., Jacksonville, Florida, U.S.A.) was used for simultaneous I-IONM. During LAR-C-IONM, vocal cord mucosa at the contralateral side of surgery was stimulated using electrodes of intubation tube on bipolar stimulation mode (Figure 9). Minimum current was given for supramaximal stimulation. Duration of this current was 0.1–1 ms, period between each stimulus was 2–4 ms and median current intensity was 8mA (3–15 mA). Stimulus frequency was 0.4–0.7 Hz. To minimize artifacts, mean value of two stimulations of reverse polarity was estimated. Signals were filtered, and signals with a bandwidth of 1.5–1000 Hz were selected and recorded for analysis. Adduction response of the vocal cord was recorded from electrodes of ETT which contacted to the vocal cord at the operation side (or contralateral to the stimulated side). LAR-C-IONM was applied by recording cR1 response through this electrode.

First response was recorded from LAR before skin incision. Adequate stimulation may not be obtained due to insufficient contact of electrodes to mucosa or secretions which block stimulus. If LAR is not obtained, ETT should be repositioned until a safe reflex is acquired. The structure assumed to be the nerve was stimulated with a current of 1–2 mA through monopolar hand probe (Medtronic Xomed, Jacksonville, FL, USA)for I-IONM.[28,32,35]

Sinclair *et al*. evaluated 134 nerves under risk of 100 patients who underwent thyroid or parathyroid surgery. Investigators mentioned that LAR-C-IONM was highly sensitive for RLN traction and compression. Nerve stress periods resulted with a decrease in compound muscle action potential (CMAP) and LAR amplitude responses as well. When the traction causing stretching on the nerve is released, decreased amplitude response in LAR-C-IONM may reverse. Investigators also defined the critical values for stimulant LAR-C-IONM in this study. They suggested to acquire actual baseline or beginning LAR responses before skin incision or before any tissue manipulation. In one-sided interventions, baseline contralateral LAR should be recorded. Contralateral LAR responses (in one-sided interventions) are used for evaluating the reason of any signal reduction intraoperatively that can be due to either real nerve stress or malposition of ETT. If beginning LAR is <150 µV, an alternative neuromonitoring method (such as I-IONM) should be used due to unreliable results of LAR-C-IONM. When the amplitude of LAR response decreases by >50% from the baseline value, tissue should be released and the surgeon should wait to avoid nerve injury. When amplitude decreases by >60% compared to the beginning values and does not recover after releasing, post-operative vocal cord dysfunction is possible. LAR is highly sensitive for stretching and LAR-C-IONM is often able to detect changes before CMAP responses are affected. If LAR amplitude decreases and does not recover to baseline amplitude after tissue is released, laryngeal PCA contraction through vagal nerve stimulation should be evaluated with laryngeal palpation.[32]

More than 60% reduction in closure amplitude compared to beginning amplitude or closure amplitude lower than 100 µV were detected significant for post-operative vocal cord paralysis(VCP) by investigators. For predicting VCP, more than 60% reduction at closure amplitude compared to beginning amplitude has a sensitivity of 85.7%, specificity of 99.2%, positive predictive value of 99.2%, and negative predictive value of 99.2%. When nerves with a beginning amplitude of <150 µV were excluded, sensitivity, specificity, positive predictive value, and negative predictive value were estimated as 100%. When closure amplitude is <100 µV, estimated sensitivity was 66.7%, specificity was 98.1%, positive predictive value was 66.7%, and negative predictive value was 98.1%. As the nerves with a beginning amplitude of <150 µV were excluded; sensitivity, specificity, positive predictive, and negative predictive values were 66.7%,100%,100%, and 98.1%, respectively. In this study, increased latency at LAR did not predict nerve injury. This condition shows that "combined events" concept that is used in C-IONM for predicting post-operative nerve paralysis may not be valid for LAR. It has been accepted that one reflex may be carried out through different sensorial and motor axonal fibers with various velocities which may contribute to the variability of LAR-C-IONM latency.[32]

In the present study, it has been reported that dissection of lower pole before dissection of upper pole and identification of RLN minimized the reduction of LAR amplitude. Thus, the surgeon initially performed lower pole dissection routinely. Traction was terminated in case of decrease more than 40% in LAR responses. Furthermore, surgical site was irrigated with warm saline solutions after the traction was terminated. It has been reported that these maneuvers decreased the total number of transient amplitude declines.[32]

In another study, Sinclair *et al*. compared data from I-IONM of 130 nerves at risk in 100 patients and data from LAR-C-IONM from 216 nerves at risk in 168 patients. Nine (6.9%) transient VCP (seven hypomobility and two immobility) in I-IONM, 2 (0.98%) transient VCP in LAR-C-IONM (p=0.004), and 1 permanent VCP (p=0.75) in each group were detected. Test benefit ratio was 5.23 for LAR-C-IONM compared to I-IONM and relative risk reduction was 81%. In I-IONM group, five of the VCP cases related to traction trauma, however, there was no case of VCP related with traction trauma in LAR-C-IONM group. Two cases of VCP occurred due to bipolar cautery in LAR-C-IONM group. Traction trauma develops stage by stage and a high percentage of injury can be prevented by C-IONM methods, however, sudden actions such as electrocauterization, clamping, ligation, or transection may not be prevented by C-IONM.[33]

Most critical advantage of LAR-C-IONM is no need for any additional probe for vagus stimulation. Bilateral vocal cord adduction can be generated by stimulating laryngeal mucosa only through the surface electrode-based ETT and LAR-C-IONM can be applied.[33] However, this technique has just started to be applied and has many limitations. Especially, surgeons have limited knowledge about LAR and its interpretation, also they do not have enough experience. Most important limitation of this technique is the applicability in medical centers which employ experienced neurophysiologist who can evaluate optimal LAR response and work in cooperation with surgeons. Important technical problems can still be encountered even in those centers.

Tubes that were used for LAR-C-IONM were not specifically produced for this monitorization. Positions of electrodes on ETT are not ideal for stimulation. Although LAR response is bilateral, recording bilateral LAR response and stimulating at the same time are not possible with currently used surface electrode-based ETT. During stimulation of one side of the tube, contralateral LAR response can be recorded. For LAR-C-IONM, ETTs both stimulating and recording bilaterally should be produced. It has been anticipated that accordingly designed ETTs can record bilateral LAR and evaluate the possibility of position changes at the same time using contralateral (opposite of the operation side) LAR. Furthermore, it has been thought that by acquiring bilateral responses, warning criteria related with decreased amplitude will be determined and evaluated better.

In future, production of equipment for LAR-C-IONM which will help surgeons for application of LAR-C-IONM alone without comprehensive monitoring systems or additional experienced team members may enable widespread application of this method.

Stimulation Electrodes For IONM

Unipolar or bipolar stimulation probes are used for nerve stimulation in IONM. By both bipolar and monopolar probes, mean depolarization rate is 100% with 1mA stimulation of RLN and appropriate EMG response can be acquired. The monopolar probe is more sensitive to localize RLN during the mapping, and bipolar probe is more sensitive to minimize the false-positive responses. Nowadays, the choice of stimulation probe mostly depends on the purpose of stimulation, characteristics of the probe, proximity to the nerve or whether there is fascia over the nerve, and preference of the surgeon.[39]

Intermittent IONM probe can give information about nerve function only for a limited time at the moment of stimulation. It does not prevent a possible injury due to dissection between two stimulations. A stimulation following dissection can give information about any possible injury. To overcome these limitations and make a real-time IONM, C-IONM is used. However, for making C-IONM, vagus nerve has to be dissected circumferentially and a probe has to be applied. During application or dislocation of this probe, a potential nerve injury may arise. Although C-IONM has an ability to predict early detection and prevention of changes that depend on traction trauma, there is a low possibility to prevent sudden actions such as clamping, electrocauterization, and transection.[40]

During dissection, stimulating hemostatic clamps (RLN systems, Inc., Neurovision SE) were used for nerve stimulation in history, but have not become widespread.[16] In an experimental study on swine models, it has been shown that stimulating dissectors were able to record suitable EMG waves after stimulations of RLN, vagus nerve, and EBSLN as monopolar and bipolar stimulation probes.[41]

Lately, seeking for a single device that is a combination of a dissector and I-IONM stimulating probe that gives an actual feedback at the moment of dissection has started again. Chiang *et al*. applied IONM on 168 nerves at risk in 100 patients with a prototype stimulating dissector which was created by connecting stimulating probe cable with handle of the dissector. There was no morbidity due to the stimulating dissector and no nerve injury because of clamping, transection, or electrocautery. Furthermore, it has been reported that this device alerted the surgeon earlier for EMG changes related to traction.[42]

Even though this is a successful method, single device is connected to the stimulation cable and changing cable and application to the devices with various types, shape and size such as scissors and dissectors may not be practical. Lately, to overcome this disadvantage, Sung *et al*. developed a stimulation cable with a magnetic tip that easily is applied to and removed from the handle of every metallic surgical instrument. Investigators reported that in human and swine subjects, this stimulation cable with a magnetic tip is safe, can be applied simply, suitably, and effectively to every surgical instrument, and provides real time feedback to the surgeon about nerve during I-IONM.[43]

Similar to that, Kim *et al*. used a stimulation cable with ring-shaped tip that can easily be applied to the surgical instruments.[44] Energy-based devices have widespread use in thyroid surgery. Stimulation cables were connected to two different energy-based devices (Harmonic Focus® [Ethicon, Somerville, New Jersey] and LigaSure™ [Covidien, Dublin, Ireland]) and applicability of energy devices with a stimulation function was evaluated experimentally in swine models and EMG data obtained were compared with EMG data through conventional probes. Investigators reported that stimulations by energy-based devices combined with stimulation probes were as safe and effective as stimulations with conventional probes. It has been reported that using these prototype devices, without a need to change the device, simultaneous surgical dissection, resection, and nerve stimulation are permitted and risk for nerve injury by energy-based devices can be reduced.[41,45]

Recently, in a study with nerve stimulating dissector (Spes Medica S.r.l., Genova, Italy), initial identification rate of RLN was faster in reoperations of thyroid gland compared to bipolar stimulating probe.[46]

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – N.A., M.K., A.I., M.U.; Design – N.A., M.K., A.I., M.U.; Supervision – N.A., M.K., A.I., M.U.; Materials – N.A., M.K., A.I., M.U.; Data collection &/or processing – N.A., M.K., A.I., M.U.; Analysis and/or interpretation – N.A., M.K., A.I., M.U.; Literature search – N.A., M.K., A.I., M.U.; Writing – N.A., M.K., A.I., M.U.; Critical review – N.A., M.K., A.I., M.U.

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