Future directions of neural monitoring in thyroid surgery

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Abstract: Intraoperative nerve monitoring is a well validated technology for use in thyroid surgery. Intermittent intraoperative nerve monitoring is commonly used. Unfortunately, it helps detect injury only after it occurs limiting its usefulness. Continuous intraoperative nerve monitoring appears to be the emerging technology which has the ability to overcome this disadvantage. In this review, we discuss the utility of continuous nerve monitoring and its application in open and remote access thyroidectomy and the role of surgeon's role in the use of these new technologies.

Keywords: Continuous intraoperative nerve monitoring (CIONM); intraoperative nerve monitoring (IONM); vagus stimulation; loss of signal; vocal cord palsy; recurrent laryngeal nerve palsy (RLN palsy)

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Introduction

This chapter discusses the current technology, techniques and guidelines in utilizing nerve monitoring during thyroid surgery with an aim to consider future directions of an established practice pattern. The current technology for continuous intraoperative nerve monitoring (CIONM) will be illustrated as well as an interpretation of the results that can be gained from using the technology. A discussion of the pros and cons, the role of the surgeon in the utilization of CIONM and surgeon experience will highlight the strengths and weaknesses of neural monitoring. The goal is to provide a road map towards the future trends in the use of this technology including endoscopic/remote access thyroid surgery and maybe even in directed ablative therapies. This article aims to provide a clear understanding of nerve monitoring, its role now and in the future.

CIONM with automated periodic stimulation (APS): technique and settings, equipment and probes used, pros, cons; current experience

Intermittent nerve monitoring is the prevalent available technology for monitoring the recurrent laryngeal nerve (RLN) function during thyroid surgery. This system has proven effective in mapping the course of the nerve during surgery but has not been proven to significantly lower the permanent injury rate. Due to the intermittent nature of monitoring, the nerve may be injured between stimulations. Traction injury which is more common than transection, occurs in a gradual manner. This may not effectively be detected by intermittent intraoperative nerve monitoring (IONM). To overcome this disadvantage, CIONM for thyroid surgery was introduced in 1997 where the RLN was proximally stimulated. In 2007, Lamadé *et al.* introduced the present technology in use by placing an electrode on the vagus nerve and using it to indirectly stimulate the RLN (1).

Technique and setting

For any patient undergoing IONM, a special endotracheal tube is used for intubation which is compatible with electrodes for monitoring. The electromyographic signal that provides both amplitude and latency is recorded. An electrode is placed on the vagus nerve in its intracervical course in the carotid sheath after circumferential dissection, taking care not to devascularize the nerve. The nerve is stimulated every 6 seconds, hence the moniker automated periodic stimulation. The strength of the stimulating current is 1 mA with a frequency of 1 Hz (usually frequency of <3 Hz). This is the chosen strength as it achieves supramaximal stimulation of A & B fibers of the vagus nerves sparing the C fibers which are responsible for most of the autonomic effects of vagal stimulation. Prior data has shown that this setting should help avoid the central, cardiac, pulmonary and gastrointestinal adverse effects of vagal stimulation (2,3).

The handheld probe for the intermittent nerve monitoring is also used to identify and map out the course of the RLN.

After placement of the electrode on the vagus nerve, the system is calibrated and a baseline response for both amplitude and latency are noted. The amplitude response should be greater than 500 microvolts (4), while the latency varies between the right and left RLN owing to the difference in the length. The right RLN has a latency between 3 to 5 milliseconds while the left RLN has a latency between 5 and 7 milliseconds owing to the variable length and course. The amplitude and latency are charted on a timeline as the procedure progresses. These initial values for amplitude are critical as they form the basis for latency calculation and help to guide dissection of the nerve and indicate when the nerve may be injured, which can help prompt suspension of surgical maneuvers.

Multiple designs of electrodes have been introduced for use with CIONM. They are broadly classified into open, closed and partially closed types depending on the mode of contact with the nerve. From a functional standpoint they are similar and aim to achieve easy applicability and removal, have a low stimulation current and provide signal stability (5). The vagus nerve is usually present in the carotid sheath posterior and in the groove between the great vessels. In a minority of cases it may be present anterior to the vessels (less than 5%) or located posterior to the carotid artery or the internal jugular vein. The variability of the vagus nerve in the carotid sheath may add to difficulty in placement of the probe or increase the chance of inadvertent displacement of the probe; a posteriorly placed vagus nerve may make probe placement difficult while an anteriorly placed vagus nerve may make identification and probe placement easy but may make it more prone to displacement.

Interpretation of results

Adherence to International Neural Monitoring Study Group (INMSG) guidelines greatly improve the reliability of the CIONM. Injury to the RLN occurs most commonly due to traction on the nerve (>80%) during thyroid surgery (6). Stress on the RLN which may cause neuropraxia is typically a gradual event during surgery. CIONM is geared to detect this event before the RLN stops functioning. The most common sites of stretch on the nerve are at the ligament of Berry and the point of intersection of RLN with the inferior thyroid artery when the thyroid lobe is retracted medially during surgery (7). As mentioned earlier, the baseline amplitude response needs to be >500 microvolts to confidently interpret the results of the monitoring as the surgery progresses.

Isolated loss of amplitude of more than 50% or a latency increase greater than 10% may be due to artifacts such as displacement or rotation of the tube or displacement of the probe and may not be predictive of injury. Combined events defined as a greater than 50% decrease in the amplitude along with greater than 10% increase in the latency is more predictive of nerve injury. A severe combined event is defined as greater than 50% decrease in the amplitude and an increase in latency by 10% in another series (6). Severe combined events resulted in vocal cord palsy and had a sensitivity of 67% and specificity of 92% to predict vocal cord palsy. However, combined events were reversible in 73% of cases, with 80% of patients not progressing to develop vocal fold palsy once the traction was released and the amplitude was allowed to recover to more than 50% of the baseline (7).

A loss of signal is defined as the drop in the amplitude to less than 100 microvolts and usually indicates vocal cord palsy. It is a good indicator of vocal cord palsy with a sensitivity of 83%, specificity of 99%, positive predictive value of 83% and negative predictive value of 98% (6). These authors suggested that if the amplitude recovered by more than 50% within 20 minutes of the event, the probability of vocal cord palsy reduced to 70%. Unfortunately, the loss of signal was reversible in only 17% of cases.

Advantages of CIONM over intermittent IONM

IONM has proven to be of utility by reducing the RLN identification time, reducing temporary vocal fold palsy rates and helping to avoid bilateral vocal fold palsy (6). The limitation of the intermittent monitoring system is the risk of injury to the nerve between two stimulations. CIONM overcomes this drawback of intermittent IONM by providing real time data which helps in avoiding injury before it occurs. Surgical maneuvers that put the RLN at risk can be immediately suspended by the visual and acoustic feedback provided by the system. A recent study demonstrated that when traction on the nerve is released when the monitoring system detected a combined event, 80% of patients did not progress to a loss of signal (8). This demonstrates the value of the system in preventing a clinical adverse event by warning the surgeon of the nerve at risk. This has the potential to prevent temporary and permanent vocal cord palsy which is a clear advantage over the intermittent nerve monitoring system.

CIONM has a good sensitivity and a high specificity in predicting vocal fold palsy. This makes it more reliable than the intermittent IONM. In addition, the false positive and false negative rates of vocal fold palsy are very low. This prevents unnecessary staged surgeries thereby reducing the cost of delivering care (8,9).

Disadvantages of CIONM

CIONM setup involves more steps than intermittent nerve monitoring. The vagus nerve needs to be dissected circumferentially for the probe placement. This may devascularize a segment of the nerve. The probe placement may be rendered tedious if it is a large goiter or if it is a revision surgery. These surgeries are considered high risk where nerve monitoring is of enhanced value. Optimal probe placement may not be possible in these scenarios thereby defeating the purpose of nerve monitoring. A recent study lists the factors that may increase the time for the probe placement—posterior position of the vagus, BMI>35, reoperative surgery, gland volume >75 mL (5). Inadvertent displacement of the probe remains a significant issue (0–40% displacement rate). This may lead to an increase in the operative time. There are isolated reports of systemic adverse effects in one series with the use of CIONM (10).

CIONM is well suited to detect a gradual injury as a result of traction. Trauma to segments of the nerve that are caused by transection, thermal injury due to energy devices, compression by surgical instruments and ligation are acute and may not be identified prior to injury or loss of signal. CIONM is geared to detect a gradual injury to the nerve and may not be useful in preventing acute trauma to the RLN. This is a major limitation.

There are factors that may decrease the reliability of the system: (I) The malposition or displacement of the endotracheal tube may result in isolated changes in the amplitude; (II) inadvertent vagal electrode displacement increases operative time and possibility of vagal trauma; (III) loose contact between the electrode and the vagus nerve resulting in a variation in the amplitude and latency; (IV) irrigation of the surgical field with cold saline has resulted in fall in amplitude and gradual increase in latency; (V) loss of signal which is associated with the use of bipolar cautery (4).

The criteria for a combined event was defined so that CIONM has high specificity to warn the surgeon of the impending danger of nerve injury while avoiding excessive warnings by the system (false positive test) which may lead to unnecessary caution while proceeding with dissection. Basarrate and group have argued that latency is not as useful a measure and using combined events as the warning threshold defeats the purpose of continuous monitoring as it reduces the sensitivity of the system. In the data presented, they report that it resulted in fewer warnings. They propose changing the amplitude threshold to <75% of baseline instead of <50% (11). The electrophysiological threshold needs to be standardized which may help in widespread adoption of CIONM.

Safety concerns of CIONM

CIONM is a newer technology compared to intermittent IONM, which has been widely accepted. CIONM uses 1 mA of current strength for stimulation as it supramaximally stimulates the A & B fibers sparing C. Groves and Brown have demonstrated that it takes more than 2 mA for stimulation of C fibers of the vagus which are responsible for the autonomic effects (12). The possible adverse effects of vagal stimulation are: central (headache), cardiac (arrhythmias), respiratory (bronchospasm) and gastrointestinal (nausea and vomiting). A 2010 study compared the intermittent IONM to CIONM and found that there was no overt sympathetic overregulation and no major adverse events related to autonomic effects of vagal stimulation (13). There have been isolated reports of hemodynamic instability due to cardiac arrhythmias and vagal neuropraxia in two patients in a study, along with multiple inadvertent displacements of the vagus nerve electrode (10). However, two large studies performed recently have not reported any adverse events with CIONM (11,14).

Given the limitations of the CIONM, various strategies have been proposed to improve intermittent IONM. Instruments used for dissection that also function as nerve stimulators have been proposed. Chiang *et al.* have used the dissecting forceps and scissors that are connected to the nerve monitor as a stimulating probe. They did not encounter an injury or adverse event because of these instruments. This may be the precursor for development of "smart" instruments in the future (15).

Current experience

In 2014, a large prospective multi institutional study with 102 patients was conducted which laid out the criteria for defining adverse events. The concept of a combined event was defined using amplitude and latency changes. A mild combined event was defined as amplitude decrease of >50% to 70% with a concordant latency increase of 5% to 10% while a severe combined event was defined as amplitude decrease of >70% with a concordant latency increase of >10%. Complete loss of signal was defined as complete loss of RLN signal amplitude to <100 microvolts. This helped in standardization so that CIONM can be used in the operating room with well-defined criteria (6).

A recent large single institution study in the United States looked at CIONM in 344 thyroidectomies where there were 455 RLNs at risk. The threshold for alarm/warning was >50% reduction in amplitude and or >10% increase in the latency. Impending injury was detected in 33 cases. Immediate release of the traction for minutes helped preserve the function of nerves. Fifteen patients had loss of signal where there was no improvement in 20 min though the nerve was anatomically intact. In five patients CIONM helped make the decision to stage the surgery. They found combined events predicted neve injury better than amplitude or latency changes individually. LOS had a positive predictive value of 100% to predict post-operative palsy and a negative predictive value of 100% in this study (14).

Another single institution study from Spain where CIONM was used in 386 thyroidectomies with 400 nerves at risk were studied found a greater than 50% drop in amplitude alone had a sensitivity of 100% and specificity of 97.7% with positive predictive value of 47% and negative predictive value of 100%. In 80% of cases where there was more than 50% drop in amplitude, suspension of traction resulted in recovery of amplitude with none of these patients having post-operative vocal cord palsy. Decrease in amplitude of more than 75% was a better predictor of post-operative vocal cord palsy than an isolated increase in latency of more than 20%.

They also found that the rate of warnings was higher in intrathoracic goiters than in thyroidectomies with central neck dissection for carcinoma which suggests increase traction on the nerve in surgeries for intrathoracic goiter (8,11,16).

Use of IONM in endoscopic/robotic thyroidectomy

IONM use in remote access thyroidectomy has been adopted from the experience with open surgery. However, the use of IONM in endoscopic/robotic thyroidectomy and adherence to International Monitoring Study Group is low (17). Unlike transcervical surgery there are no accepted standards for the use of IONM in this setting. Intermittent IONM is more commonly used than CIONM. The approach and identification of the nerve differs in endoscopic thyroidectomy. The external branch of the superior laryngeal nerve is not routinely visualized and stimulated in endoscopic thyroidectomy especially the transoral endoscopic thyroidectomy vestibular approach (TOETVA). The superior and deep orientation of the nerve and the angle of dissection typically protect it. The RLN is approached and visualized from above and is identified close to its point of insertion. Various probes with modification have been used in the intermittent IONM. Ball tip probe, flexible wire probe, cautery hooks, dissecting instruments and percutaneous puncture techniques to deliver the probe into the operative field have been used (18-23).

A recent review reported that intermittent IONM is the dominant technology used today in endoscopic thyroidectomy (17). The reported rates of temporary RLN injury was in the range of 0% to 3.6% and permanent RLN injury was in the range of 0% to 0.4%.

The feasibility of Continuous IONM in TOETVA has been demonstrated. Real-time monitoring of the RLN is the advantage over intermittent IONM as it helps suspend maneuvers that may put the nerve at risk. CIONM may be combined with intermittent IONM as the nerve is not identified at its usual location and approach as in transcervical surgery. The main disadvantage of CIONM in TOETVA is that the vagus nerve is not routinely in the operative field and requires additional dissection potentially adding to the operative time. Vagal dissection may also lead to injury. This contributes to the reluctance of surgeons to use CIONM for monitoring (24).

Surgeon's role in the use of new monitoring technology

As surgeons, we need to be aware that not all RLNs that are anatomically intact and lose signal with concomitant loss of vocal fold motion, recover completely (8). There is a greater than 70% chance that patients will develop vocal fold impairment in case of an abnormal signal though the nerve is anatomically intact (25). There may also be a false negative rate whereby a good signal with IONM leads to poor vocal fold motion. INMSG in their 2016 meeting in Boston, USA, presented their preliminary results from a multicenter prospective study, for Identification of False Negative causes in electromyography (EMG) monitored thyroid surgery, called IFAN. Other studies have demonstrated a few cases of false negative rate whereby patients had vocal fold impairment post-operatively despite strong IONM signals intraoperatively. The false negative rate using IONM needs to be further studied, and extended to CIONM. Overall, there is value in minimizing any morbidity due to loss of vocal cord function even if it is temporary. Hence, adopting CIONM technology which holds promise to reduce injury is advantageous as long as safety is guaranteed.

The use of nerve monitoring technology in novel technologies such as radiofrequency ablation (RFA) and other ablative techniques has not been studied but is something worth conceptualizing. RFA and other ablative techniques like ethanol ablation and laser ablation of thyroid nodules, are becoming the newest way to treat benign and malignant thyroid nodules without surgical excision (26,27). Ablation studies have demonstrated promising results, but one of the concerns regarding RLN proximity and injury during these techniques may lead some to consider nerve monitoring during these minimally invasive procedures. Early attempts at ablation of thyroid and parathyroid lesions were met with unacceptably high rates of injury. The current nerve monitoring technology utilizes an endotracheal tube and either stimulation or direct electrode application to either the RLN or vagus. An ability to percutaneously monitor the RLN or vagus during ablation of thyroid nodules may advance the adoption or utilization of these novel technologies. This may be the future for nerve monitoring and the next direction for research in the field.

Conclusions

In conclusion, the true incidence of temporary and permanent vocal fold palsy is underestimated. The role of IONM in its current forms, both intermittent and continuous monitoring systems, is to provide real-time information on the status of nerve function during dissection that can decrease the morbidity of vocal fold motion impairment post-operatively. The advantages and disadvantages of intermittent and continuous nerve monitoring systems have been described, with the hopes that continuous nerve monitoring may be the improved version to help in preventing vocal fold palsy. Further, as remote access approaches to the thyroid gain popularity, and minimally invasive ablative techniques that may provide an alternative to thyroid surgery altogether, IONM may add an additional layer of safety to protect the nerve. At present, the gold standard remains direct identification and dissection of the RLN, but the next steps in future research to advance this technology may change that.

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Footnote

Conflicts of Interest: RP Tufano: Consultant, Medtronic. The other authors have no conflicts of interest to declare.

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