Review Article

Neural monitoring in thyroid surgery is here to stay

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Abstract: The iatrogenic injury of the recurrent laryngeal nerve (RLN), more clinically significant than those affecting the external branch of the superior laryngeal nerve (EBSLN), constitute one of the most feared perioperative complications of thyroid surgery and parathyroid glands, in terms of impact in clinical and economic-social costs. Moreover, these events rank among the leading reasons for medicolegal litigation of surgeons because of its attendant reduction in quality of life. The average incidence of RLN paralysis, permanent and temporary, after thyroidectomy is high and stands between 2.3% and 9.8% respectively. Given the elements described above, it is essential for the surgeon to adhere to a carefully standardized intraoperative technique that minimizes the possibility of RLN injuries. Intraoperative neuromonitoring (IONM) was introduced to reduce RLN injuries and for this reason, it achieved considerable success among endocrine surgeons. However, even today it is considered an adjunct device to the direct identification of the RLN. In this perspective, IONM of RLN constitutes an important aid, since it represents a reliable tool for the evaluation of functional neural integrity. Despite the ever-increasing diffusion of the IONM, prospective randomized studies are needed for further validation. The purpose of this work is to analyze scientific evidence to show that IONM in thyroid surgery is here to stay.

Keywords: Intraoperative neuromonitoring; thyroid surgery; vocal cord palsy; recurrent laryngeal nerve (RLN)

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The preliminary consideration is that the intraoperative anatomical direct identification of the recurrent laryngeal nerve (RLN) remains the "gold standard" in endocrine surgical technique and intraoperative neural monitoring (IONM) is a useful tool in facilitating this identification, also providing neurophysiological data complementary to the visual identification itself, since anatomical integrity does not always correspond to the functional one.

IONM has emerged in the last two decades, as one of the main avenues of progress within endocrine surgery. The idea of applying IONM techniques traditionally used in neurosurgery and neurophysiology within the endocrine operating room is definitely not novel, since the first experiences of IONM in thyroid surgery draw back to 1970s.

The advantage IONM reported in the literature indeed is due to the possibility of recognition of RLN, differentiating it from other tissues. It implies some significant potential benefits: firstly, neuromonitoring allows the visual and sound feedback of the inducible potentials, to avoid surgical operations that could potentially damage the nerve function. This last aspect would assume greater relevance in the case of continuous neuromonitoring of the vagal nerve where, compared to intermittent neuromonitoring, there is the perception of nerve suffering while it is occurring, thus allowing the surgeon to change strategy and to interrupt risky surgical maneuvers. Secondly, the IONM allows recording on paper and computer archiving systems the electromyographic signals pre- and post-mobilization of thyroid lobes, providing valid legal protection. Furthermore, IONM favors the localization of the exact location of the injury along the course of the nerve, allows young surgeons to approach thyroid surgery more safely, provides the possibility of identifying anatomical variants that can cause neural damage, if not found beforehand.

IONM is aimed at either identifying functional RLN which cannot be recognized purely on the basis of anatomical landmarks (mapping) or to continuously assess the functional integrity of neural pathways which can be injured during surgery (monitoring): thus, IONM aims to enhance the standards on RLN management in thyroid surgery (i.e., nerve identification and exposure).

As can be easily deduced, the macroscopically evident anatomical injury during the surgical procedure is the one attributable to the direct section of the nerve, a much less frequent occurrence than others. It is therefore clear that most of the possible damage to the RLN (due to traction, clips, thermal damage, by energy-based devices used) is not identifiable during surgery and that this implies that the potential benefit obtained by integrating direct anatomic identification with the evaluation of neural functionality, provided by neuromonitoring, appears indisputable.

Today, there are IONM endocrine scientific societies, such as the International Neural Monitoring Study Group, the Korean, German, Turkish, Latin America, Italian neural monitoring study groups, for IONM in thyroid and parathyroid surgery whose members are dedicated to IONM in their daily clinical and research practice. These international scientific societies established guidelines, credentials, training requirements, experimental research for endocrine practice of IONM. The spectrum of IONM expertise in this endocrine monitored surgery varies across different Countries, but there is no doubt that the driving force is not limited to European Countries, America, and Asia and involves, today all Continents.

IONM has place as training program for residents too.

Nicely, in some settings there is a nice idea of a different professional figures (endocrine surgeon, anesthesiologist and clinical neurophysiologist) working hand in hand in the endocrine operating room and advising the thyroid surgeon about the surgical strategy and RLN function.

Is IONM evidence based in thyroid surgery?

Although the advantages of the IONM appear to be intuitive, according to the literature the evidence in their its favor is anything but easily deducible. Although many attempts have been made in recent years to statistically demonstrate the reliability of IONM as an essential tool for RLN identification, individual clinical studies have produced conflicting results and meta-analyses have yet to establish a uniformly acceptable conclusion (1). We must first consider how the low incidence of the endpoint in question (the frequency of temporary and permanent recurrent paralysis) determines the need for studies with high sample numbers to reach an adequate statistical power. Secondly, we must consider also the inhomogeneity that characterizes many of the studies published: in fact it is known that certain conditions increase the probability of the occurrence of peri-procedural neural damage and represent risk factors to be weighted when drawing up eligibility criteria for patients to be enrolled in clinical trials in order to avoid selection bias. Specifically, the rate of recurrent paralysis can be linked to the type of pathology treated, the surgery, as well as the type of training/surgical experience level of the surgeon. A final observation to make is relative to the final endpoint: if the majority directs the analysis to the laryngoscopic finding of vocal fold paralysis (VFP), some refer to the quality of the voice after surgery, a parameter that is less easily measurable and that often also requires the functional evaluation of EBSLN.

If on one hand several studies conducted in the last years confirm that IONM should not be incorporated into the standard of care for thyroid surgery (2-4), analyses conducted by Wong *et al.* (5), Yang *et al.* (6), Zheng *et al.* (7) demonstrated the opposite, in that there were significant benefits of IONM use. In the last 5 years among the observational studies conducted, three deserve greater relevance. Snyder *et al.* (8) conducted a retrospective analysis of 3,435 at-risk nerves evaluating the impact of IONM on surgical outcome over time. The authors observed a remarkable reduction in the rate of neuronal damage after 20 months from the beginning of the use of IONM, emphasizing specifically the role of IONM in the identification of anatomical variants and difficult dissections.

Barczyński *et al.* (9) in 854 patients, who underwent redo thyroidectomy, tried to verify the hypothesis that in such cases IONM reduces the prevalence of RLN injuries. The authors documented rates of 2.6% of transient paralysis and 1.4% of permanent paralysis in the IONM group compared to 6.3% of transient paralysis and 2.4% of permanent paralysis in the group without IONM.

To test the potential advantages of IONM in surgical training, Alesina *et al.* (10) analyzed the operative outcome of 1116 thyroidectomies performed by information surgeons: of these, only less than a third were performed using IONM while for the remaining the young surgeon he was supervised by an experienced endocrine surgeon. The rate of recurrent paralysis in the two groups was similar, and the authors concluded that IONM seems to offer the surgeon in training a safety comparable to that of an experienced surgeon.

A study by Sturgeon *et al.* (11) indicate that approximately 37% of surgeons, routinely or in select cases use, IONM during thyroid procedures. IONM use, according to Sanabria *et al.* (12) and Barczyński *et al.* (13) is also stratified based on equipment availability, experience, and surgeon age.

To raise the levels of scientific evidence, meta-analyses have also been carried out, of which the one conducted by Pisanu *et al.* best represents what currently exists in the literature. In this meta-analysis twenty studies comparing thyroidectomy with and without IONM were reviewed: three prospective, randomized trials, seven prospective trials, and ten retrospective, observational studies. Overall, 23,512 patients were included, with thyroidectomy performed using IONM compared with thyroidectomy without IONM (visual alone VA group). The total number of nerves at risk was 35,513, with 24,038 nerves (67.7%) in the IONM group, compared with 11,475 nerves (32.3%) in the VA group. The rates of overall RLN palsy per nerve at risk were 3.47% in the IONM group and 3.67% in the VA group. The rates of transient RLN palsy per nerve at risk were 2.62% in the IONM group and 2.72% in the VA group. The rates of permanent RLN palsy per nerve at risk were 0.79% in the IONM group and 0.92% and in the VA group. None of these differences were statistically significant, and no other differences were found. The meta-analysis conclude with no statistically significant difference in the incidence of RLN palsy when using IONM versus VA during thyroidectomy. However, these results must be approached with caution, as they were mainly based on data coming from non-randomized observational studies. Further studies including high-quality multicenter, prospective, randomized trials based on strict criteria of standardization and subsequent clustered meta-analysis are required to verify the outcomes of interest (14).

Thus, the question is if IONM in thyroid surgery evidence-based? IONM is not based on class I evidence. In general, no IONM technique (neurosurgery, orthopedics, etc..) has class I evidence. Studies are limited to class II and III reports. IONM should be recognized at same level of evidence applied to most our clinical practice within thyroid surgery. However, the level of EBM in IONM is not worse than that found in thyroid surgery generally. Furthermore, class I studies will ever occur as the likelihood of preventing RLN deficit using IONM, the incidence of permanent RLN complications are low. In the future, the benefit of IONM will continue to be based on good clinical outcomes, historical control studies, and cost-benefit evaluations.

Appraisal

Reluctance to use IONM has significantly changed in the last years, together with an increasing acknowledgement of the usefulness of IONM in endocrine surgery practice. Some resistance to the use of IONM still exists nowadays and relies mainly on the criticism that the use of IONM is not evidence-based. Today the use of IONM is supported by the possibility it offers in verifying the functional integrity of RLN, which cannot be verified in any other way during the surgical procedure. This information provided to the surgeon is of indisputable value and help. In fact the goal of monitoring modalities is to detect surgical or physiological insults to the RLN while they are still reversible or, in cases where prevention is not an option, to minimize the damage done to these structures during thyroidectomy (15,16). All the advantages related to its use explain the increasing number of monitored procedures and the indication, by guidelines, of its use and although further randomized trials would be useful to further clarify the topic, perhaps it would not be ethically correct to have the patient choose to undergo surgery without IONM. Finally, constant technological innovation in all surgical disciplines constantly calls for the introduction of new devices and techniques also for IOMN, such as the anterior laryngeal electrodes (ALEs), which provide similar and stable electromyographic responses with equal sensitivity for recording evoked responses during neural monitoring in thyroid and parathyroid surgery and offer significantly more robust monitoring of EBSLN (16,17).

The definition of progress involves of the process of gradually getting nearer to achieving something or completing something, an advance or movement to an objective or toward a goal. IONM and more recently, and especially continuous mode of IONM application is an advance to an object because of (I) optimization of nerve control during dissection; (II) close the interval between IONM results and pre- and postoperative assessment of vocal cord movement, voice quality, breathing and swallowing (16).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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