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Original research

Double probe intraoperative neuromonitoring with a standardized method in thyroid surgery

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ABSTRACT

Introduction: The purpose of this study was to evaluate the effectiveness of intraoperative neuromonitoring (IONM) of the recurrent laryngeal nerve (RLN) and the vagus nerve (VN) with a standardized approach in thyroid surgery.

Methods: Retrospective study with an experimental group with which IONM was used, both with the RLN that the VN, and a control one, each consisting of 300 total thyroidectomies. Each patient underwent a pre-and post-operative videolaryngoscopy. The number of RLNs identified and the number of transient and permanent RNL injuries for each group were assessed, and then compared with χ^2 tests. In the experimental group Sensitivity, Specificity, Positive Predictability, Negative Predictability and Accuracy of IONM were evaluated, depending on the number of true positive results, false negatives, true negatives and false positives obtained by comparing the results of IONM with the post-operative videolaryngoscopies.

Results: The results obtained for the experimental group vs. the control group were: RLNs identified 595 (99.1%) vs. 552 (92%) -P Value <0.0001; Permanent RLNs injuries 4 (1.33%) vs. 5 (1.67%) -P Value 1; transient RLNs injuries 1 (0.33%) vs. 8 (2.67%) -P Value 0.044.

The IONM system, for the RLN and VN showed respectively: Sensitivity 66.7% vs. 83.3%; specificity 97.6% vs. 99.5%; Positive Predictability 22.2% vs. 62.5%; Negative Predictability 99.6% vs. 99.3%; Accuracy 97.3% vs. 99.3%.

Conclusions: Our study highlights that using IONM with a standardized method in thyroid surgery, improves the ability to identify the RLN and a reduction in the incidence rate of transient RLN injuries.

1. Introduction

Damage to the recurrent laryngeal nerve (RLN) is the most severe specific complication that can occur in thyroid surgery, and underlies major medical-legal controversies among endocrine surgeons [1–3].

The incidence of RLN damage in thyroid surgery is highly variable depending on operator experience, with rates of incidence ranging from as low as 0.2% in specialized centers to as high as 20% in settings where thyroid surgery is infrequent [2,4,5].

Two main factors can reduce the risk of RLN injury: operator experience and a systematic search to allow visualization of the RLN [1,2,4,5]. Nevertheless, the incidence rate of RLN damage is never zero even in the most expert hands. RLN localization is considered the most reliable means of minimizing the incidence rate of RLN damage. Hence, several intraoperative neuromonitoring (IONM) systems have been introduced in recent years including that of the continuous monitoring of the vagus nerve [6–11].

One IONM system available on the market, the Avalanche XT (Dr. Langer Medical GmbH – Waldkirch – Germany), involves the application of current pulses to tissues that induce a release of muscular action potentials from muscles innervated by the pulsed nerve. This system is equipped with two probes; a unipolar probe with a detection radius that is sufficiently wide to allow one to search for nerves that are not visible even after lobe dislocation, thus guiding dissection maneuvers, and a bipolar probe with a smaller detection radius that allows one to identify structures (such as nerves or other structures) by recording electrical conduction. The Avalanche XT system was purchased by the 5th Division of General Surgery and Special Surgical Techniques of the Second University of Naples in July 2010.

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2. Methods

We conducted a retrospective case–control study including all the total thyroidectomies performed between 1 October 2009 and 31 October 2011 at the 5th Division of General Surgery and Surgical Special Techniques of the Second University of Naples.

The only criteria for exclusion from the study was the diagnosis, during pre-operative videolaryngoscopy, of a pre-existing vocal cord paralysis (every patient who is subjected to total thyroidectomy in our Department is subjected to both a preoperative and postoperative videolaryngoscopy undertaken by otolaryngologists of the Otorhinolaryngology Clinic of the Second University of Naples).

Each operation was performed by the same surgical team.

Between 1 October 2009 and 31 July 2010, 306 total thyroidectomies without IONM were carried out: 6 patients were excluded from the study for vocal fold paralysis due to previous thyroid surgery preoperatively so the control group consisted therefore of 300 total thyroidectomies.

Between 1 September 2010 and 31 December 2010, 100 total thyroidectomies with IONM Avalanche XT were carried out: these patients were not included in the study because they were considered as part of a "learning curve".

Between 1 January 2011 and 31 October 2011, 302 total thyroidectomies were carried out using IONM with Avalanche XT: 2 patients were suffering from paralysis of one vocal cord due to previous thyroid surgery and were excluded. The Avalanche group consisted of 300 total thyroidectomies.

In each group 600 nerves were therefore considered to be at risk.

The two groups were homogeneous in terms of age, sex, and type of pathology necessitating this operation (Table 1). Each group was in turn divided into a low-risk class, which included only non-toxic multinodular goiters (LR Avalanche subgroup and LR Control subgroup), and a high-risk class, which included all risky conditions represented by reoperation due to bilateral recurring goiters, thyroid cancers (in these cases we performed total thyroidectomy and bilateral prophylactic central-compartment neck dissection and, when necessary, therapeutic lateral neck compartmental lymph node dissection) [12–17], toxic multinodular goiters, Graves' disease, thyroiditis associated with non-toxic multinodular goiter and substernal goiters [3,18–22] (HR Avalanche subgroup and HR Control subgroup).

The Avalanche Group was composed of 152 low-risk patients (LR Avalanche subgroup) and 148 high-risk patients (HR Avalanche subgroup), including 234 women and 66 men; they had a mean age of 50.57 years (range 17–80 years old).

The Control Group was composed of 157 low-risk patients (LR Control Group) and 143 high-risk patients (HR Control Sub-group), including 227 women and 73 men; they had a mean age of 50.10 years (range 22–78 years old) (Table 1).

Although the influence of curarizing drugs with a long half-life on the evoked muscular action potential is not totally clear [4,23,24], to reduce the potential for bias, patients in the Avalanche group were subjected to general anesthesia in the absence of long half-life curarizing drugs and intubated with traditional oro-laryngeal tubes onto which an adhesive electrode was applied before the intubation. During the operation, we used a unipolar probe on each side until one or more structures considered to be the RLN were detected. To ascertain their nature, the structures were then examined using a bipolar probe while recording. Once each RLN was located, the electrical conduction of the RLN was tracked before completion of the lobe dissection (R1) and again at the end of the operation (R2).

On each side, the neurovascular bundle of the neck was prepared for a 2-cm span, and the vagus nerve conduction track was recorded using the unipolar probe before starting the lobe dissection (V1) and then again at the end of the operation (V2). The action potential evoked from vagal nerve stimulation should reduce the risk of false negatives (FNs) that can be caused by stimulation of the RLN at a distal point with respect to the site where the damage might have occurred. Stimulation was performed at a pulse current of 1 mA and a frequency of 3 Hz.

The frequency with which the recurrent nerves were located was compared between the groups. We carried out a $\chi 2$ test on two independent samples because this test allows nominal variables to be compared; hence, it is considered the only valid test for the comparison of frequencies. We created contingency tables characterized by m lines (nominal variables) and n columns (samples being examined). The nominal variables are represented by the number of recurrent nerves located, the number of permanent RLN paralyzes observed, and the number of temporary RLN paralyzes that occurred. The two samples are represented by the Avalanche Group and by the Control Group respectively. The null hypothesis H0 for this study was that the samples and variables examined were independent. Our alternative hypothesis was that the samples and the nominal variables were inter-dependent. The lower the probability is of rejecting H0 when it is true, the more significant is the test result. The adopted level of significance (α) was 5%.

Modification or disappearance of electrical conduction at R2 and V2 was evaluated relative to that at R1 and V1 for the RLNs and vagus nerves respectively. Subsequently, we evaluated the correspondence or non-correspondence of the eventual modification of the intra-operative electromyographic signal and vocal cord motility detected during the post-operative videolaryngoscopy.

The cases where a reduction or loss of the signal was recorded were considered to have a positive test result: a true positive (TP) if the post-operative videolaryngoscopy documented paralysis of the vocal cords, and a false positive (FP) if the videolaryngoscopy excluded alterations in the vocal cord motility. When no signal modification or loss was recorded, the test result was considered to be negative: a true negative (TN) when the videolaryngoscopy

Table 1
Demographic data, indication for surgery and details of groups and subgroups.

		Avalanche group ($n = 300$)	Control group ($n = 300$)	Statistical test	*P*-value
	Age	50.57 (range 17–80)	50.1 (range 22–78)	Z- test	0.628
	Sex (F/M Ratio)	234 F/66 M (3.55/1)	227 F/73 M (3.11/1)	$\chi 2$	0.498
	Disease				
Low risk patients	Non toxic multinodular goiter	152 (50.67%)	157 (52.33%)	$\chi 2$	0.682
	Thyroid carcinoma	44 (14.66%)	49 (16.33%)	$\chi 2$	0.572
High risk patients	Substernal goiter	39 (13%)	34 (11.33%)	$\chi 2$	0.532
	Toxic multinodular goiter	38 (12.67%)	31 (10.33%)	$\chi 2$	0.37
	Graves' disease	8 (2.67%)	11 (3.67%)	$\chi 2$	0.484
	Thyroiditis	12 (4%)	8 (2.67%)	$\chi 2$	0.362
	Recurrent goiter	7 (2.33%)	10 (3.33%)	$\chi 2$	0.46

reported normal cord motility and a false negative (FN) when an alteration in cord motility was detected. Based on this classification, we evaluated the sensitivity, specificity, positive predictability (PP), negative predictability (NP) and accuracy (*A*) of the IONM system. Sensitivity was calculated by applying the formula TP/(TP + FN); specificity was calculated by applying the formula TN/(TP + TN); PP was calculated by applying the formula TP/(TP + FP); NP was calculated by applying the formula TN/(FN + TN) and A was calculated by applying the formula (TP + TN)/TOTAL.

Each parameter was evaluated separately (stimulation of the RLN and of the vagus nerve) and compared. The patients for whom post-operative videolaryngoscopy revealed paralysis of the RLN were then subjected to further videolaryngoscopic examination 1, 3, and 6 months post-operatively, in order to differentiate permanent from temporary paralyzes. Paralysis that persisted 6 months post-operatively was considered permanent.

3. Results

In the Avalanche group, 595/600 (99.17%) RLNs were located. Of the 5 nerves that could not be located, 3 were not found on the left (2 in the HR subgroup and 1 in the LR subgroup), and 2 on the right (1 in the HR subgroup and 1 in the LR subgroup). In the control group, we were able to locate 552/600 (92.0%) RLNs. Of the 48 nerves that could not be located, 28 were not found on the left (18 in the HR subgroup and 10 in the LR subgroup) and 20 on the right (14 in the HR subgroup and 6 in the LR subgroup).

For the 5 RLNs that were not located in the Avalanche group, post-stimulation nervous conduction tracks were absent (R1 and R2), although they were present and unaltered in the vagus nerves (V1 and V2). In all five cases, post-operative videolaryngoscopy showed normal cord motility; therefore they were considered to be FPs in the RLN stimulation analysis with TN vagus nerve stimulation results.

For the 48 RLNs that were not located in the Control Group, postoperative videolaryngoscopy showed 1 vocal cord with permanent paralysis on the right side in a patient who underwent total thyroidectomy for Graves' disease (HR Control Subgroup).

In the Avalanche group, 4/300 (1.33%) operations resulted in permanent RLN paralysis (2 in the LR subgroup, 1 on the right and 1 on the left; and 2 in the HR subgroup, 1 on the right and 1 on the left). In the Control group, 5/300 (1.67%) operations resulted in permanent RLN paralysis (2 in the LR subgroup, 1 on the right and 1 on the left; and 3 in the HR subgroup, 1 on the right and 2 on the left). In the Avalanche group, 1/300 (0.33%) operations resulted in temporary RLN paralysis (in the HR subgroup, on the right). In the Control group, on the other hand, 8/300 (2.67%) of the operations resulted in temporary RLN paralysis (2 in the LR subgroup, 1 on the right and 1 on the left; and 6 in the HR subgroup, 2 on the right and 4 on the left).

Our statistical analysis of two independent samples with a $\chi 2$ test revealed that the RLN was located more frequently in the Avalanche group than in the Control group ($p < 0.0001$). Additionally, RLNs were located more frequently in the LR Avalanche subgroup than in the LR Control subgroup ($p = 0.002$), and more frequently in the HR Avalanche subgroup than in the HR Control subgroup ($p < 0.0001$) (Table 2).

The very high degree of significance in the HR subgroup comparison suggests that the IONM system was particularly useful in high-risk operations. Our analysis indicated that temporary damage of the RLN was reduced dramatically in the Avalanche group relative to the Control group ($p = 0.044$), whereas the incidence of permanent damage of the RLN did not differ significantly between the two groups ($p = 1$) (Table 3).

Table 2
Identified RLNs in each group and subgroup.

	Individuated RLNs	*P*-value
Avalanche group (nerves at risk = 600)	595 (99.17%)	
Control group (nerves at risk = 600)	552 (92%)	<0.0001
LR Avalanche subgroup (nerves at risk = 304)	302 (99.34%)	
LR Avalanche subgroup (nerves at risk = 314)	298 (94.90%)	0.002
HR Avalanche subgroup (nerves at risk = 296)	293 (98.99%)	
HR Avalanche subgroup (nerves at risk = 286)	254 (88.81%)	<0.0001

In the Avalanche group, the IONM system yielded 4 TPs, 14 FPs, 580 TNs, and 2 FNs with respect to RLN location. In contrast, we obtained 5 TPs, 3 FPs, 591 TNs, and 1 FN for vagus nerve location. Consequently, our RLN detection had a sensitivity of 66.7%, a specificity of 97.6%, a PP of 22.2%, an NP of 99.6%, and an A of 97.3%. For detection of the vagus nerve, the values were as follows: sensitivity 83.3%, specificity 99.5%, PP 62.5%, NP 99.8%, and A 99.3% (Table 4).

4. Discussion

Perioperative RLN lesions usually result from functional damage being incurred while the nerve is anatomically intact, though nerve dissection does occur infrequently [3,18,25,26].

Functional damage of an intact nerve can be caused by improper ligature, thermal dispersion during hemostasis or excessive traction. There is a particularly high risk of excessive traction (20–50%) when there are exposed nerves that bifurcate before entering the larynx. In this circumstance, the anterior motor branch may adhere closely to Berry's ligament and therefore be at high risk of being stretched during lobe dislocation [3,18,19].

Two main factors can reduce the risk of RLN injury: operator experience and a systematic search to allow visualization of the RLN [1,2,4,5].

Nevertheless, the incidence rate of RLN damage is never zero even in the most expert hands. RLN localization is considered the most reliable means of minimizing the incidence rate of RLN damage. Hence, several intraoperative neuromonitoring (IONM) systems have been introduced in recent years with the aim of helping surgeons locate nerves, especially in the most risky conditions, such as that of a non-recurrent inferior laryngeal nerve, recurrent goiter, thyroid cancer (i.e., indicating lymphadenectomy), thyroiditis, Graves' disease, toxic multinodular goiter or substernal goiter [2,18–22]. Although many technical and technological improvements have been achieved, IONM systems are not infallible.

Studies testing IONM system utility and efficacy have reported conflicting results, apparently due to differences in the sensitivity and specificity of nerve recognition, as well as discrepancies concerning the actual reduction of the incidence of temporary and permanent nerve damage [2,5,19,20]. Some authors examining IONM systems have reported a reduction in temporary RLN paralysis only, whereas others have reported (statistically non-significant) trends toward reduction in both temporary and permanent paralysis, or permanent paralyzes only, while still others did not detect any differences [2–4,21,22,27–30].

Table 3
Temporary and permanent recurrent laryngeal nerve paralysis in the two groups.

	Avalanche group ($n = 300$)	Control group ($n = 300$)	*P*-value
Temporary RLNs paralysis	1 (0.33%)	8 (2.67%)	<0.044
Permanent RLNs paralysis	4 (1.33%)	5 (1.67%)	1

Table 4
IONM Sensitivity, Specificity, Positive Predictivity, Negative Predictivity and Accuracy relative to RLN and Vagus detection and videolaryngoscopic outcomes.

Avalanche system applied to:	Recurrent laryngeal nerve	Vagus nerve
Sensitivity	66.7%	83.3%
Specificity	97.6%	99.5%
Positive predictivity	22.2%	62.5%
False predictivity	99.6%	99.8%
Accuracy	97.3%	99.3%

The present results confirmed that use of a double probe IONM system enabled us to locate the RLN with a much higher frequency than a visual search alone. This benefit was apparent in both low-risk and high-risk cases, though the effect was more pronounced in the HR subgroup, which included patients being treated for thyroid cancer, toxic multinodular goiter, Graves' disease, thyroiditis, substernal goiter and recurrent goiter. It is worth noting that we found the neuromonitoring system to be particularly useful because it allowed us to readily locate two inferior non-recurrent laryngeal nerves (both on the right side), which, due to their configuration, might have been confused with vascular structures and therefore left susceptible to damage.

The improvement in our ability to locate the RLN using the IONM system was associated predominantly with a reduction in the incidence of temporary, rather than permanent, RLN damage. The discrepancy in the results between the rates of permanent vs. temporary paralysis raises an important question. That is, if the location of the nerve occurs much more frequently when neuromonitoring is applied, why is the rate of permanent damage not reduced as well? And why is the rate of temporary damage so dramatically reduced? To resolve these questions we need to understand the mechanisms underlying the lesions [3,18,19,25,26].

Damage due to nerve dissection is rare and occurs more frequently when the nerve is anatomically intact. However, in cases where there is nerve bifurcation with the anterior branch (generally the motor branch) being tightly adherent to Berry's ligament, the posterior branch can be mistaken for the whole nerve, leaving the unidentified motor anterior branch at risk of damage [3,18,19]. Additionally, even if the operator recognizes this specific anatomical situation and continues to search for the motor branch, traction on the lobe is more intense and extended in duration, which also places the nerve at risk of being stretched. With neuromonitoring, however, when the sensory branch is stimulated at a site that is distal to the emergence point of the motor branch, no (or a very low) potential is observed. This lack of potential tells the operator that only the posterior sensory nerve branch, rather than the whole nerve, has been located and thus that s/he needs to proceed with ample caution in the search for the anterior motor branch. Additionally, the use of a unipolar probe, which has a wider detection range, in an IONM system enables the zone where the nerve runs to be located more easily and more quickly than with visual inspection alone, thus reducing the time and force needed to medialize the lobe in search of nerve structures, and ultimately reducing exposure of the nerve to axon elongation.

The above benefits of neuromonitoring may explain the reduced incidence rate of temporary damage we observed, but do not explain why the rate of permanent damage was not significantly reduced. In the Avalanche group, permanent RLN lesions occurred with the nerve anatomically intact. Three of these lesions occurred when hemostasis was particularly complicated due to prolonged bleeding of perineural vessels and a subsequent repeated need to coagulate them with bipolar forceps. Therefore, it seems that, in these cases, permanent nerve damage was due to lateral dispersion of thermal energy as a consequence of the need to repeat the hemostasis in close proximity to the nerve.

We did obtain some FPs with the IONM system. Neuromonitoring of the RLN was applied at the visible point nearest to the upper thoracic outlet, since it is known that stimulation at a more distal point can generate FNs if a lesion is produced proximal to the point being examined. Stimulation at this level might be invalidated by the interposition of thin perineural tissues, whose presence can interfere with the pulse current supply. Alternatively, and more likely, the motor branch may emerge from the nerve at a point that is even more proximal to the one being stimulated.

The FPs which were recorded with vagus nerve stimulation could be explained by functional fatigue of the neuro-myotransmission system. Intensive stimulation at relatively short time intervals might have induced the nerve to become refractory to electrical stimulation, impeding the axons' abilities to reach the necessary threshold for action potential generation, or may have impeded anterograde axonal propagation. Another possibility is temporary synaptic "fatigue" as intensive neurostimulation might have led to a temporary depletion of pre-synaptic vesicular acetylcholine content or to a down-regulation of post-synaptic acetylcholine receptors. In either circumstance, an electromyographic signal would fail to develop and, as a consequence, stimulation of the nerve, even if intact and functioning, might not produce a recordable response.

Since FNs occurred with anatomically intact nerves in absence of neurotmesis, we can deduce that the nature of the damage was functional. This type of damage can occur only if the nerve develops a phlogosis after a physical insult. Such inflammation would be expected to be the biological basis of any subsequent functional damage. There is a delay between a physical insult, the development of a phlogosis and its damaging effect. During this delay period, the nerve can continue to show normal electrical condition, giving the appearance of an unchanged IONM result, and therefore a FN.

Another cause may be the trauma from intubation, which can cause paralysis of a vocal cord, even in the absence of objective signs of trauma via the postoperative videolaryngoscopy [31–36]. In this case obviously the nervous track would be preserved (IONM), while the vocal cord would be paralyzed (videolaryngoscopy), thus determining a FN.

The use of IONM cannot always prevent neurological damage to the vocal cords, due to the existence of FPs and FNs. However, the results of the present study indicate that RLN localization before and after thyroid resection using a double probe IONM with a standardized method and confirmation of vagus nerve conduction tracks can be extremely useful for two reasons. Firstly, it increases the operator's overall ability to locate RLNs. Secondly, it yields a significant reduction in the incidence of temporary nerve damage. Hence, given the results provided by our study, we can recommend the extensive use of IONM with a standardized technique as a routine application in thyroid surgery.

Ethical approval

None.

Author contribution

Massimo De Falco: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Giuseppe Santangelo: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Santolo Del Giudice: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Gallucci Federica: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Umberto Parmeggiani: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

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