Acta Biomed 2022; Vol. 93, N. 2: e2022040 DOI 10.23750/abm.v93i2.11178

Original article

Intraoperative Neuromonitoring, Nerves at Risk and Staged Thyroidectomy, our Experience on 377 Consecutive Cases

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Abstract. *Purpose:* The aim of this study was firstly to report the experience of intermittent intraoperative neuromonitoring (I-IONM) and evaluate the impact of loss of signal (LOS) in staged thyroidectomy management. *Methods:* We retrospectively reviewed patients who underwent total thyroidectomy, performed by a single surgeon in two years. All patients have been subjected to I-IONM. In case of intraoperative loss of signal (LOS), planned total thyroidectomy was always aborted. Six-month follow-up was performed. Postoperative dysphonia was evaluated with VHI-10 score in 3 time settings T1, during hospital stay, T2 after 30 days, T3 after 6 months. Dysphonia has been compared to IONM results to evaluate sensitivity and specificity. *Results:* 377 patients were included. Incidence of dysphonia was calculated based on the number of nerves at risk (NAR). We evaluated a total of 724 NAR. LOS encountered were 43 cases (5.9% of total NAR), of these 14 were LOS 1 while 29 were LOS 2. 27 patients (3.7% of NAR) presented early post-operative dysphonia with VHI-10 score > 13 (T1), among these 16 had presented LOS at IONM (true positives) while11 had no LOS (false negatives). In T2 and T3 we reported a decrease in true positive cases increasing false positives. Sensitivity at T3 reached 85.7% while specificity and odds ratio were respectively 94.8% and 110. *Conclusions:* Given the high sensitivity and specificity, IONM should be considered a useful tool for thyroid surgery and its use should be suggested for patients undergoing planned total thyroidectomy. Its right application may cancel the risk of bilateral paralysis. (www.actabiomedica.it)

Key words: IONM, intraoperative neuromonitoring, thyroidectomy, staged thyroidectomy, vocal cord palsy, RLN

Introduction

Recurrent laryngeal nerve (RLN) injury with postoperative dysphonia is one of the most relevant and serious complication after thyroid surgery and it is the first cause of legal dispute. Preoperative indications are involved in the process that lead to RLN injury. RLN nerve injury can still occur because of anatomical variation, surgeon inexperience, revision surgery (2–30%) and high-risk situations including retrosternal/mediastinal large goiters or Graves' disease, and invasive malignancy (1). Transient palsies of RLN are observed in 3–8%, permanent postoperative RLN injury occurs approximately in 0.2–6.6% (2–6). Clinical manifestations of unilateral RLN injury depend on degree of nerve injury. The symptoms associated to RLN palsy have an important impact on the patient's quality of life comprehending incomplete laryngeal closure during swallowing, cough, impaired phonation, dyspnea and aspiration pneumonia (3-7).

Bilateral RLN palsy is rare (0.2–0.6%) but it is a life-threatening situation leading to a potential lethal airway obstruction (7,8).

During superior pedicle dissection the external branch of the superior laryngeal nerve (EBSLN) can be injured most frequently. Injuries of EBSLN determine changes in the quality of the voice leading to a highest/lowest pitches limitation. The incidence of EBSLN injury ranges from 0 to 58% (9–12).

To minimize the risk of nerval injury is mandatory the intraoperative identification of nerves and adequate capsular dissection. Intraoperative identification of nerves alone can't prevent nerval injury.

To prevent nerval injury several identification systems were introduced. Intermittent intraoperative neuromonitoring (I-IONM) of RLN was introduced for the first time in 1966. Monitoring of both evoked and spontaneous electromyographic (EMG) activity of vocalis muscle was expected to substantially reduce the rate of RLN injury.

IONM allows the identification of the RLN before visualization during operations and at the end of surgical procedure evaluating the functional integrity of the RLN (13).

Several scientific societies recommend the use of IONM especially in case of revision surgery, bilateral surgery procedures, pre-existing RLN paralysis to prevent bilateral vocal cord palsy and improve the identification of RLN in difficult cases (14,15).

Nowadays the advantages of routine use of IONM remains still debated. Despite initial enthusiasm for IONM, most studies have failed to prove a significant difference in the incidence of RLN injury between IONM and visualization alone. IONM has not resulted in a decrease in the paralysis rates, but I-IONM may result in a change to a two-stage thyroidectomy in case of loss of signal after the first lobectomy (16–19).

The aim of this study was firstly to report the experience of I-IONM in a reference center and evaluate the impact of loss of signal (LOS) in the management of staged thyroidectomy in patients with initially planned total thyroidectomy.

2. Matherials and Methods

We retrospectively reviewed patients who underwent total thyroidectomy at Department of Surgery of Parma University Hospital from 1 January 2018 until 31 November 2019 with institutional review board approval, an informed consent was obtained from all participants, during the consent all the patients were informed about the possibility of stage procedure and how this would differentiate the postoperative period and planning of their treatment.

Inclusion criteria: patients with a planned total thyroidectomy (Traditional total thyroidectomy, open mini-invasive thyroidectomy-OMIT, Mini-Invasive Video-Assisted Thyroidectomy-MIVAT) both for benign and malignant disease according to the ATA Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (20).

The intermittent intraoperative neuromonitoring (I-IONM) was performed in every surgical procedure by a disposable nerve stimulator (NIM 3.0 Nerve Monitoring System, Medtronic, Minneapolis, Minnesota, USA) according to the International Neural Monitoring Study Group Guidelines (15).

A preoperative indirect laryngoscopy was always performed to evaluate vocal cord function, we included only patients with normal cord function.

Exclusion criteria: patients with personal history of previous thyroid, cervical and larynx surgery, patients with pre-existing vocal cord dysfunction, patients with initially planned hemithyroidectomy or extended lymph nodal dissection or concomitant parathyroid surgery, intraoperative neuromonitoring conducted with C-IONM.

In all cases, standard IONM procedures were strictly followed, and EMG signals (V1-S1-R1-R2-S2-V2) were obtained and registered at each step.

The vagus nerve has been stimulated after dissection of the carotid sheath increasing the stimulation level up to 3 mA without dissecting carotid sheath. During the lateral retraction of the upper pole of the thyroid lobe EBSLN has been searched with a stimulation level of 1 mA.

The dissection of upper pole capsule and the tertiary branches of the inferior thyroid artery enables identification of the RLN that has been searched with a stimulation level of 1 mA. After lobectomy the final testing of EBSLN, RLN and vagus nerve were always performed.

If intraoperative signal of the vagal or recurrent laryngeal nerve fails or the EMG drops below 100 μV

after resection of the first lobe IONM trouble shooting algorithms were applied: loss of initial satisfactory EMG signal (< 500 μV); No EMG response with stimulation at 1-2 mA for RLN and 3-4 mA for nerve vagus; low response < 100 μV with stimulation at 1-2 mA; no laryngeal twitch. If LOS was confirmed after the application of IONM trouble shooting algorithms the planned total thyroidectomy was always aborted (21,22).

LOS have been differentiated between type 1 (LOS1), corresponding to a segmental lesion of laryngeal nerve, while type 2 lesions (LOS 2) have been considered nerve's global lesions including non-conductive vagus nerve. Contralateral lobectomy, for oncological reasons (R1 resections, lymph-vascular space invasion, extracapsular neoplastic invasion), was planned after vocal cord function evaluation with direct laryngoscope during postoperative management.

Six-month follow-up was performed for all patients included in this study.

After surgery patient's dysphonia has been evaluated as clinical practice routine for a 6-months period. In patients with LOS and postoperative dysphonia clinically suspected Italian Voice Handicap Index 10 (VHI-10) was applied in 3 different time settings: T1 during hospital stay; T2 after 30 days; T3 after 6 months. VHI-10 score >11 was considered abnormal (23,24) (Tab. 1).

Indirect laryngoscopy has been performed only in patients with a pathological VHI-10 score after T2 time. Categorical variables were evaluated by applying the Chi square test while the numerical variables were evaluated by applying Mann-Whitney test. Sensitivity, specificity, efficiency, false positive (subjects with LOS and normal postoperative vocal cord function), false negative (the presence of an adequate EMG during surgery and postoperative vocal cord dysfunction), positive predictive value (PPV refers to the probability that subjects with LOS at the completion of surgery will have vocal cord dysfunction postoperatively) and negative predictive value (NPV refers to the probability that subjects with maintenance of adequate EMG at the completion of surgery will have normal postoperative vocal cord function) (23,24), positive likelihood

Table 1. VHI-10 (Voice Handicap Index-10) questionnaire

	Questions	
1	My voice makes it difficult for people to hear me La mia voce e' udita con difficolta dalla gente	0 1 2 3 4
2	People have difficulty understanding me in a noisy room La gente ha difficolta a capirmi in una stanza rumorosa	0 1 2 3 4
3	My voice difficulties restrict my personal and social life Le mie difficolta di voce restringono la mia vita personale e sociale	0 1 2 3 4
4	I feel left out of conversations because of my voice Mi sento tagliato fuori dalle conversazioni a causa della mia voce	0 1 2 3 4
5	My voice problem causes me to lose income I miei problemi di voce mi fanno guadagnare di meno	0 1 2 3 4
6	People ask, "What's wrong with your voice?" La gente mi chiede "Cosa c'e che non va con la tua voce?"	0 1 2 3 4
7	I feel as though I have to strain to produce a voice Mi sembra di dovermi sforzare per produrre la voce	0 1 2 3 4
8	The clarity of my voice is unpredictable La chiarezza della mia voce e imprevedibile	0 1 2 3 4
9	My voice problem upsets me Il mio problema di voce mi sconvolge	0 1 2 3 4
10	My voice makes me feel handicapped La mia voce mi fa sentire handicappato	0 1 2 3 4

TAB 1 –Instructions: 0 = never, 1 = almost never, 2 = sometimes, 3 = almost always, 4 = always. Istruzioni: 0 = mai, 1 = quasi mai, 2 = a volte, 3 = quasi sempre, 4 = sempre.

ratio, negative likelihood ratio, and diagnostic odds ratio were calculated with a confidence interval (CI) determined at 95% level (25,26).

All factors deemed to be statically significant present a P values < 0,05.

Statistical analysis was performed with SPSS 25.0 (IBM SPSS statistics).

The study has been approved by our institution independent ethics committee (Comitato etico AVEN – area vasta Emilia nord).

3. Results

In the study were included 377 patients, including 294 women (77.9%) and 83 men (22.1%). The average age of the patients was 54.5 years (27-85). Among these 347 underwent planned total thyroidectomy (92%), while in 30 cases the contralateral completion procedure was aborted for LOS (8%), hemithyroidectomy was performed in these cases.

Mean operative time was 58.2 minutes (30-120) with a mean postoperative hospital stay of 2.04 days (1-6). The definitive histological results are listed in Table 2.

Among all the patients 150 (39.7%) had thyroiditis evidenced by preoperative ultrasound or by postoperative histology, while 48 patients (12.7%) had preoperative hyperthyroidism.

The incidence of dysphonia was calculated based on the number of nerves at risk. We evaluated a total of 724 nerves at risk (NAR). The total number of LOS encountered was 43 cases out of the total number of NAR (5.9%). 14 were LOS 1 (segmental lesion of laryngeal nerve), while 29 were LOS 2 (nerve's global lesions including non-conductive vagus nerve). Twentyseven patients (3.7% among NAR) presented early postoperative dysphonia T1 (considering its duration up to discharge, maximum hospital stay: 3 days). At T1 patients with dysphonia presented a VHI-10 score always > 11 (range 11-29). In this group of dysphonic patients 16 had presented LOS at IONM (true positives) while 11 had not presented alterations during neuromonitoring (false negatives). The remaining 27 patients presenting LOS (3.7%) are considered as false positives, 19 LOS 2 and 8 LOS 1 (VHI-10 score < 11) (Tab. 3).

Of the 27 patients with early dysphonia (T1) only 19 (2.6%) had dysphonia at 30 days (T2) without supportive therapy, VHI-10 score ranges from 11 to 30 for patients who complained dysphonia at T2, the other 8 patients with dysphonia at T1 presented a VHI-10 score < 9 at T2. At 6 months (T3) only 7 patients (0.9% of total NAR) presented dysphonia (VHI-10 score

Table 2. Indications to surgery (MNG – multinodular goiter)

Diagnosis	*Number*	*%*
Follicular carcinoma	1	0.3%
Papillary carcinoma	129	34.2%
Medullary carcinoma	1	0.3%
MNG	205	54.3%
Basedow disease	25	6.6%
Other	16	4.3%

Table 3. IONM results related to clinical dysphonia occurrence in T1 (evaluation during post-operative hospitalization)

T1	***Number***	***%***
True Positive	16	2.3%
False Positive	27	3.7%
True Negative	670	92.5%
False Negative	11	1.5%

Table 4. IONM results related to clinical dysphonia occurrence in T2 (evaluation at 30 day follow up)

T2	***Number***	***%***
True Positive	11	1.5%
False Positive	32	4.4%
True Negative	673	93%
False Negative	8	1.1%

Table 5. IONM results related to clinical dysphonia occurrence in T3 (evaluation at 6 months follow up)

T3	***Number***	***%***
True Positive	6	0.9%
False Positive	37	5.1%
True Negative	680	93.9%
False Negative	1	0.1%

Table 6. VHI-10 score results related to LOS and hystological findings at T1-T2-T3

Postoperative diagnosis	*LOS 1*	*LOS 2*	*No LOS*	*T1*	*T2*	*T3*
Papillary carcinoma	5	10	4	8.42±7.42 (1-21)	6.73±7.1 (1-25)	3.42±1.12 (1-12)
MNG	8	17	6	12.6±8.5 (2-29)	10.7±9 (1-30)	7.1±7.8 (1-30)
Basedow	1	2	1	10±9.4 (2-22)	7.5±6.45 (2-16)	2.25±1.25 (1-4)

TAB 6 – VHI-10 score at T1-T2-T3 has been reported as median ± DS and range.

Table 7. Statistical results of I-IONM application related to clinical dysphonia occurrence in T1

T1	*%*	*CI 95%*
Sensitivity	59.26%	38.80%-77.61%
Specificity	96.13%	94.41%-97.43%
Efficiency	94.75%	92.87%-96.26%
Predictive Value of Positive Test	37.21%	22.98%-53.27%
Predictive Value of Negative Test	98.38%	97.13%-99.19%
Likelihood Ratio of Positive Test	15.297	9.4250-24.8296
Likelihood Ratio of Negative Test	0.4238	0.2689-0.6681
Odds ratio	36.0943	15.2940-85.1837

Table 8. Statistical results of I-IONM application related to clinical dysphonia occurrence in T2

T2	*%*	*CI 95%*
Sensitivity	57.89%	33.50%-79.75%
Specificity	95.46%	93.65%-96.87%
Efficiency	94.48%	92.55%-96.02%
Predictive Value of Positive Test	25.58%	13.52%-41.17%
Predictive Value of Negative Test	98.83%	97.70%-99.49%
Likelihood Ratio of Positive Test	12.7549	7.6478-21.2727
Likelihood Ratio of Negative Test	0.4411	0.2603-0.7475
Odds ratio	28.9180	10.8823-76.8446

ranges from 12 to 30), 3 of them had a total resumption of speech with logopedic therapy (Tables 4, 5).

VHI-10 score was statistically significant higher in multinodular goiters than papillary carcinomas (P <0.05) (Tab. 6).

Table 9. Statistical results of I-IONM application related to clinical dysphonia occurrence in T3

T3	*%*	*CI 95%*
Sensitivity	85.71%	42.13%-99.64%
Specificity	94.84%	92.96%-96.34%
Efficiency	94.75%	92.87%-96.26%
Predictive Value of Positive Test	13.95%	5.30%-27.93%
Predictive Value of Negative Test	99.85%	99.18%-100%
Likelihood Ratio of Positive Test	16.6100	10.7424-25.6826
Likelihood Ratio of Negative Test	0.1506	0.0245-0.9247
Odds ratio	110.2703	12.9388-939.1717

Considering dysphonia as the major diagnostic variable in three-time settings T1-T2-T3 we evaluated IONM for sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratio, odds ratio, as highlighted in Table 7, Table 8 and Table 9.

Patients presenting LOS have been evaluated compared to patients without LOS for indication to surgery, specimen histology, age, sex, presence of thyroiditis, presence of hyperthyroidism, hospital stay and major nodule side. Among all the parameters evaluated, the only ones with statistical significance were: the age of the patients was greater in LOS + group, about 10 years older (62.35 33-85 VS 53.494 27-84, P <0.05), operative time was shorter in LOS+ group (52.5 30-95 VS 60.128 30-235, P <0.05).

The same study was carried out to evaluate possible differences between the group of dysphonic patients in T2 and asymptomatic patients with results comparable to the LOS group; statistically significant differences were found only with regard to the operative times with shorter time values in patients presenting with

Table 10. LOS cases who underwent completion thyroidectomy

Postoperative diagnosis	*Gender*	*Age*	*Surgery*	*los*	*thyroiditis*	*iperfunction*	*Early disphonia*	*30 days disphonia*	*6 months disphonia*	*Clinical recovery*	*Hospital stay*	*Completion Thyroidectomy*
Papillary carcinoma	F	45	EmiTx	1	No	No	Yes	Yes	No	/	1	Yes
Papillary carcinoma	F	68	EmiTx	2	Yes	No	No	No	No	/	2	Yes
Papillary carcinoma	F	44	EmiTx	2	No	No	No	No	No	/	2	Yes
Papillary carcinoma	F	52	EmiTx	1	No	No	No	No	No	/	2	Yes
Papillary carcinoma	M	43	Emitx	1	No	No	No	No	No	/	1	Yes

TAB. 10 – (EmiTx – emithyroidectomy, TxTot – Total Thyroidectomy).

dysphonia (47.778 30-85 VS 59.880 30-235, P <0.05). Among patients presenting LOS, only 5 completion hemithyroidectomy were performed for oncological reasons (extracapsular invasion from follicular variant of papillary thyroid carcinoma), an indirect laryngoscopy before completion surgery showed a normal ipsilateral vocal cord function.

In accordance with the patients in the other cases completion surgery was not performed because benign histology or in case of malignancy (no presence of R1 resections, lymph-vascular space invasion and extracapsular neoplastic invasion) where strict follow-up has been planned.

The Table 10 summarizes the data regarding patients with LOS who underwent completion thyroidectomy.

4. Discussion

The introduction of IONM in clinical practice is gaining acceptance and supplements the gold standard method of visual identification. IONM improve surgical outcome giving the surgeon more confidence during surgery (28-30).

In the present study we set data according to symptoms evolution (T1: 2 days; T2: 30 days; T3: 6 months) and the possible lesions type (LOS1; LOS2). Twenty-seven patients complained early postoperative dysphonia (VHI-10 score >11), only 7 cases of dysphonia were considered as permanent (during follow-up VHI-10 score was always > 11 at T1-T2-T3). Dysphonia rate (1.8%) was stackable to literature (6,31).

Bilateral RLN injuries weren't documented, in case of LOS the planned contralateral thyroidectomy was always aborted. We modified the surgical plan in 30 cases where hemithyroidectomy was performed due to LOS. Only 55 patients needed a contralateral thyroidectomy for oncological reasons, an indirect laryngoscopy before completion surgery showed a normal ipsilateral vocal cord function.

Our statistical analysis showed an increasing high rate of false positive from T1 to T3, resulting in a lower specificity of IONM (however over 94%). The high rate of false positive may be related to manipulation and traction on nerve. Non-definitive lesions of the nerve, resulting from stretching or manipulation, may lead to an intraoperative LOS without postoperative clinical symptoms onset or with a transitory nervous trauma leading to quickly recovering dysphonia (32,33).

LOS and high false positive rate can also be associated to several potential pitfalls of IONM use such as equipment malfunction (tracheal tube dislodge, defect in the device or electrodes), improper setup of equipment and anatomic variations of RLN. IONM trouble shooting algorithms should be always applied to reduce false positive LOS (21,34,35). This could moreover explain the low PPV highlighted by our data. In

literature PPV ranges from 12% to 88%, this variation, as demonstrated by recent IONM guidelines, could be related to a poor adherence to IONM management instructions (36).

Three patients suffered from transient dysphonia without LOS, and so have been considered as false negative, this could be related to non-neurological causes of dysphonia such as laryngeal complications during endotracheal intubation, or possibly by a wrong use of IONM (6,37).

We found a poor sensitivity of IONM at T1 growing to a sensitivity of 85.71% in T3. NPV ranges from 98.3% to 98.8%, this result is encouraging for IONM usefulness and still stackable to literature findings (90-100%) (38–42).

All the patients with vocal cordal palsy during laryngoscopy in T2 have been confirmed as true positive at T3, while patients without cordal palsy have been just clinically revalued at T3.

IONM can detect nerve lesions and consequently reduce bilateral paralysis aborting contralateral surgery. As assumed when a LOS occurs after the application of IONM trouble shooting algorithms at the end of the first lobectomy in planned total thyroidectomy, the application of staged thyroidectomy algorithm is strongly recommended in order to avoid bilateral injuries. Given the guidelines indications, the excision of contralateral side should be considered only in particular cases, such as complete recover of ipsilateral nerve palsy or in malignant disease interesting contralateral lobe. In case of benign thyroid disease, eventual completion thyroidectomy, increases risk of bilateral paralysis without real improvements on patients' health. In case of unifocal tumor without extracapsular extension and lymph nodes metastasis or vascular invasion a strict follow-up is strongly recommend while in case of multifocal cancers or extracapsular invasion completion surgery should be performed (43,44). Given the high sensibility and specificity IONM must be considered a useful tool for thyroid surgery and should be considered for all patients undergoing planned total thyroidectomy. IONM doesn't reduce nerve paralysis but its right application may cancel the risk of bilateral paralysis guiding the planning of staged thyroidectomy. Furthermore, in our experience, its routine use may help the surgeon to recognize RLN in hardest intervention to feel a better safety and can be considered a tool for young surgeons training. We are confident on further productions of practical and theoretical guidelines that will improve and regulate IONM use. We think that in the hands of an expert surgeon, IONM can become a highly specific tool, capable of guiding thyroid surgery towards an era where complications are even rarer, and the surgeon can always decide the best for the patient. Limitations of the present study: sample number of patients, postoperative laryngoscopy not routinely used.

Funding: This research received no external funding

Conflicts of Interest: The authors declare no conflict of interest

Author Contributions: Conceptualization: Matteo Rossini, Paolo Del Rio; Project administration: Matteo Rossini, Paolo Del Rio; Investigation: Tommaso Loderer, Elena Bonati; Data Curation. Matteo Rossini, Federico Cozzani, Tommaso Loderer, Mario Giuffrida; Formal analysis: Matteo Rossini, Mario Giuffrida; Writing – Original draft . Matteo Rossini, Mario Giuffrida, Paolo Del Rio; Visualization: Federico Cozzani, Elena Bonati; Writing review & editing: Paolo Del Rio

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Received: 27 December 2020
Accepted: 12 January 2021
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