Interpretation of intraoperative recurrent laryngeal nerve monitoring signals: The importance of a correct standardization

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HIGHLIGHTS

- Intraoperative neuromonitoring is highly predictive of the postoperative nerve function.
- Standardization permits high sensitivity and negative predictive value, but also specificity and positive predictive value.
- In selected patients with loss of signal the surgical strategy can be reconsidered.
- This study failed to demonstrate a statistically significant decrease in the nerve paralysis rate.
- Further studies are needed to better evaluate the real benefit of this technique.

ABSTRACT

Introduction: Despite the increasingly broad use of intraoperative neuromonitoring, review of the literature and clinical experience confirms there is little uniformity in application of and results across different centers. The aim of this study was to evaluate the ability of intraoperative neuromonitoring with a standardized evaluation of the signals to predict the postoperative functional outcome and its role in reducing the postoperative recurrent nerve palsy rates.

Methods: 2365 consecutive patients underwent thyroidectomy by a single surgical team: in 1356 patients (group A) with intraoperative neuromonitoring, in 1009 (Group B) without it.

Results: In group A a loss of signal was observed in 37 cases: we had 29 true positive cases, 1317 true negative, 8 false positive, and 2 false negative. Accuracy was 99.26%, positive predictive value 78.38%, negative predictive value 99.85%, sensitivity 93.55%, and specificity 99.4%. 29 unilateral nerve paralysis were observed (2.13%), 23 (1.69%) transient and 6 (0.44%) permanent. In group B 26 unilateral paralysis were observed (2.57%), 20 (1.98%) transient and 6 permanent (0.59%) Differences were not statistically significant.

Conclusions: Intraoperative neuromonitoring is highly predictive of the postoperative nerve function. We obtained a very high sensitivity and negative predictive value, but also a good specificity and positive predictive value. For these reasons, in selected patients with loss of signal, the surgical strategy can be reconsidered. On the other hand, this study failed to demonstrate a statistically significant decrease in the nerve paralysis rate. Further studies are needed to better evaluate the real benefit of this technique.

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1. Introduction

Postoperative dysfunction of the recurrent laryngeal nerve (RLN) is the most serious, sometimes irreversible and life-quality declining, complication in thyroid surgery [1]. Intraoperative identification of the RLN is a well established technique to reduce the incidence of postoperative RLN palsy [1–4].

Numerous methods have been proposed to detect the RLN during thyroid surgery [1,5]. Intraoperative neuromonitoring (IONM) has gained widespread acceptance as an adjunct to the gold standard of visual nerve identification [2,3,6,7].

In general, the technique of IONM can be used in two different situations:...
ways in thyroid surgery: firstly, for detection of the RLN during dissection and, secondly, for IONM of the RLN function [1].

In some studies the use of IONM in combination with visual RLN identification resulted in statistically significant lower post-operative RLN palsy rates than after RLN identification without IONM [1]. An evidence-based literature review of non-randomized studies looking at rates of nerve paralysis with and without monitoring with more than 100 nerves at risk showed divergent results [7]. A randomized study of Barczynski [2] demonstrated statistically lower rates for transient paralysis with IONM as compared to visual identification alone [2,7]. In the meta-analysis by Higgins [8] and in the recent one by Pisanu [9], IONM and identification alone did not demonstrate a statistically significant difference in the incidence of RLN palsy.

Rates of IONM use have recently become more or less equivalent between general surgical and otolaryngology-trained surgeons, with approximately 40%-45% in both groups using IONM in some or all cases [7]. Within the United States, monitoring appears to be used by younger surgeons and surgeons with more than 100 cases per year [5,7,10]. Moreover, IONM is now the standard of care in Germany: 90% of surgical departments were equipped with nerve monitors in 2010 [10,11].

Despite this increasingly broad use of IONM, review of the literature and clinical experience confirms there is little uniformity in application of and results from IONM across different centers [7,10]. A recent standardization of IONM methods and reporting was undertaken in an effort to provide uniformity and to minimize inappropriate variations in the applications of IONM [79].

The aim of this study was to evaluate the ability of IONM with a standardized evaluation of the signals to predict the postoperative functional outcome and its role in reducing the postoperative RLN palsy rates.

2. Materials and methods

Between June 2007 and December 2013, 2365 consecutive patients underwent thyroidectomy by a single surgical team. 2038 patients were submitted to a total thyroidectomy, 265 to a total thyroidectomy with VI level lymphectomy, and 62 underwent a completion total thyroidectomy. In this group diagnosis was benign in 891 patients multinodular goiter (37.6%), in 706 differentiated carcinoma (29.8%), in 480 Hashimoto’s thyroiditis (20.2%), in 256 Graves’ disease (10.82%), and in 32 medullary carcinoma (1.3%).

Histological diagnosis and surgical procedures are summarized in Table 1.

In differentiated carcinoma, lymph node metastasis were found in 61 patients (9.62%) and micrometastasis in 14 (1.89%). Totally lymph node metastasis were observed in 75 patients (10.16%).

The study was approved by the Bioethics Committee of the University of Cagliari. All patients provided written informed consent for the intervention and for the storage and use of their data.

All operations were performed by three experienced endocrine surgeons, with a standard Kocher’s incision. All patients were submitted to preoperative and postoperative laryngoscopy.

The recurrent laryngeal nerves were routinely identified by visualization and completely exposed. IONM was performed in 1356 patients on the basis of the availability of the equipment (2712 nerves at risk). All these patients underwent general anesthesia and were intubated with Nerve Integrity Monitor Standard Reinforced Electromiography Endotracheal Tube (Medtronic Xomed). The tube was placed with the middle of the blue-marked region (3 cm of the exposed electrodes) well in contact with the true vocal cords under direct laryngoscopy. When the monitor was well set up, we routinely checked the impedance of electrodes. A Prass monopolar stimulation probe (Medtronic Xomed) was used for nerve stimulation during thyroidectomy. Electromyographic activity was recorded on a NIM-response 2.0 or 3.0 monitor (Medtronic Xomed). No muscle relaxants were used after the skin flaps were elevated.

The neuromonitoring device was used in various phases of the operation: at the beginning a stimulation was done to the level corresponding to the vagus nerve to ensure that the monitoring system was working; after, to the structure believed to be attributable to the inferior laryngeal nerve; at the end, to the level of both the vagus (indirect stimulation) and the recurrent nerve (direct stimulation) after the removal of thyroid and the complete hemostasis of the surgical field and was used for predicting the postoperative outcome.

LOS (Loss of signal) was defined as an electromyography change from initial satisfactory electromyography, no or low response (i.e. 100 μV or less) with stimulation at 1–2 mA with dry field, and no laryngeal twitch and/or observed glottic twitch.

Patients in which the IONM did not function properly were excluded from the study.

We compared patients who have had IONM and patients who have undergone surgery with nerve visualization alone.

Patients in which IONM was utilized (group A) were 1356 (2712 nerves at risk), 322 male and 1034 female. 1171 (86.35%) were submitted to a total thyroidectomy, 40 (2.94%) to a completion total thyroidectomy and 145 (10.69%) to a total thyroidectomy associated with VI level lymphectomy. In this group diagnosis was benign multinodular goiter in 514 (37.91%) patients, differentiated carcinoma in 413 (30.46%), Hashimoto’s thyroiditis in 262 (19.32%), Graves’ disease in 150 (11.06%), and medullary carcinoma in 17 (1.25%).

Patients in which IONM was not utilized (Group B) were 1009 (2018 nerves at risk), 170 male and 839 female. 867 (85.93%) were

<table>
<thead>
<tr>
<th>Group</th>
<th>Total n (%)</th>
<th>Total thyroidectomy n (%)</th>
<th>Completion thyroidectomy n (%)</th>
<th>Total thyroidectomy + lymphectomy n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>1356 (100%)</td>
<td>1171 (86.35%)</td>
<td>40 (2.94%)</td>
<td>145 (10.69%)</td>
</tr>
<tr>
<td>Multinodular goiter</td>
<td>514 (37.91%)</td>
<td>471 (91.63%)</td>
<td>13 (2.53%)</td>
<td>30 (5.84%)</td>
</tr>
<tr>
<td>Differentiated carcinoma</td>
<td>413 (30.46%)</td>
<td>297 (71.91%)</td>
<td>22 (5.33%)</td>
<td>94 (22.76%)</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>262 (19.32%)</td>
<td>245 (93.51%)</td>
<td>4 (1.53%)</td>
<td>13 (4.96%)</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>150 (11.06%)</td>
<td>145 (96.67%)</td>
<td>0 (0.67%)</td>
<td>4 (2.67%)</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>17 (1.25%)</td>
<td>13 (76.47%)</td>
<td>0 (0.0%)</td>
<td>4 (23.53%)</td>
</tr>
<tr>
<td>Group B</td>
<td>1009 (100%)</td>
<td>867 (85.93%)</td>
<td>40 (3.96%)</td>
<td>102 (10.11%)</td>
</tr>
<tr>
<td>Multinodular goiter</td>
<td>377 (37.36%)</td>
<td>340 (90.19%)</td>
<td>20 (5.31%)</td>
<td>17 (4.51%)</td>
</tr>
<tr>
<td>Differentiated carcinoma</td>
<td>293 (29.04%)</td>
<td>218 (74.4%)</td>
<td>7 (2.39%)</td>
<td>68 (23.21%)</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>218 (21.61%)</td>
<td>197 (90.37%)</td>
<td>12 (5.5%)</td>
<td>9 (4.12%)</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>105 (10.51%)</td>
<td>103 (97.17%)</td>
<td>1 (0.94%)</td>
<td>2 (1.89%)</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>15 (1.49%)</td>
<td>9 (60%)</td>
<td>0</td>
<td>6 (40%)</td>
</tr>
</tbody>
</table>
submitted to a total thyroidectomy, 40 (3.96%) to a completion total thyroidectomy and 102 (10.11%) to a total thyroidectomy associated to a VI level lymphectomy. In this group diagnosis was benign multinodular goiter in 377 (37.36%) patients, differentiated carcinoma in 293 (29.04%), Hashimoto’s thyroiditis in 218 (21.61%), Graves’ disease in 106 (10.51%), and medullary carcinoma in 15 (1.49%).

Groups were homogeneous for characteristics of patients, diagnosis and type of surgery.

We define “transient” an injury in which the motility of the vocal cords recovered within 12 months after surgery.

Parameters were tested using the chi-square test. A logistic regression analysis was fitted using transient and permanent palsy as measurements of outcome. A p value of less than 0.05 was considered to be significant. Statistical analysis was done with SPSS software (SPSS in, Chicago, III).

3. Results

In group A a LOS was observed in 37 cases: we had 29 true positive cases, 1317 true negative, 8 false positive and 2 false negative. Accuracy of IONM was 99.26%, positive predictive value 78.38%, negative predictive value 99.85%. Sensitivity was 93.55% and specificity 99.4%. (Table 2).

29 unilateral RLN paralysis were observed (2.13%), 23 (1.69%) transient and 6 (0.44%) permanent. In this group of patients a bilateral RLN palsy was observed in two cases (0.14%) requiring a tracheostomy. Totally in group A 31 RLN injuries were observed (2.28%), in 25 cases (1.84%) transient and in 6 (0.44%) permanent. In group B 26 unilateral RLN paralysis were observed (2.57%), 20 (1.98%) were transient and 6 permanent (0.59%); bilateral palsy was observed in 2 cases (0.19%), in one patient a vocal cord recovered completely three months after surgery. The patient, which has had a completion thyroidectomy, had an unilateral palsy by previous surgery. In the other case, the patient required a tracheostomy and the lesion was permanent. Totally in group B 28 RLN injuries were observed (2.77%), 21 (2.08%) transient and 7 (0.69%) permanent.

Differences between the two groups were not statistically significant (Table 3).

The mean postoperative hospital stay was 2 days for both groups.

RLN paralysis in the two groups in relation to type of surgery and histology are reported in Table 3. Differences were not statistically significant.

No complications were attributable to the use of IONM.

4. Discussion

The incidence of RLN palsy varies from less than 1% to as high as 20%, depending on the type of disease, the type of surgery, the extent of resection, the surgical technique and the surgeon’s experience [12]. The identification of the laryngeal nerves can be difficult in patients undergoing re-operation or operations for thyroid cancer, hyperthyroidism, substernal goiter, thyroïditis, in cases of previous radiotherapy, or in presence of anatomic variants [3,12–16].

The use of IONM in thyroid surgery has gained increasing acceptance among endocrine surgeons because of several intraoperative advantages, and it has recently been well standardized [7,9].

Postoperative neural function prediction with IONM is associated with uniform and high negative predictive values ranging from 92% to 100%, but the outcome on vocal cord status is extremely unpredictable when there is a LOS at the end of a thyroidectomy because of the low positive predictive value of the procedure, which is around 33%–37.8% varying greatly from 10% to 90% [2,4,7,9]. This means that two-thirds of nerves with a missing signal can expect normal vocal cord function after surgery [9]. So, an absent or abnormal IONM signal failed to predict reliably a postoperative recurrent laryngeal nerve palsy [1]. This failure may be due to problems with the technical device, tube malposition, improper monitoring hardware connections, wrong application by the performing surgeon or continuous relaxation during the operation, resulting in an absent IONM signal [1,17]. The relative low sensitivity and positive predictive value is one of the major concerns in the use of IONM. Strict criteria of standardization can reduce technical pitfalls, thereby improving the positive predictive value of IONM [7,9]. The standardization of this technique is still not fully applied; for example, novice monitoring surgeons underuse vagus stimulation during IONM [7]. A recent Italian survey [10] revealed that participants had few experience with the standardized approach of IONM technique: the overall response rate for the correct application of the procedure was 28% [10]. For this reason, we have evaluated our results obtained applying a strict standardization of the technique.

To our knowledge, this is the largest mono-institutional study published in the literature to date. With a strict standardization of the technique we obtained a very high accuracy (99.26%), negative predictive value (99.85%), and specificity (99.4%); these data are in line with those reported in the literature. Also the sensitivity was high (93.55%), while the positive predictive value, although lower (78.38%), was significantly higher than the values reported in the literature, confirming the validity of the standardization applied. Probably the large number of procedures completed by the same team, and the fact that the technique has been applied routinely led to these excellent results. Unfortunately, our study failed to demonstrate a statistically significant decrease in RLN paralysis rates. But even this fact is widely reported in the literature and has multiple explanations.

The main weakness with this and other studies on this topic is just the inadequate power to identify a statistical difference and this is a significant limitation. The patients were not randomized which could lead to bias, but the number of patients is very large, and the groups are very well matched. Various studies have attempted to explain the difficulty to obtain statistically significant results in the use of IONM. Dralle [18] have suggested that a researcher would need 9 million patients per arm for benign multinodular goiter and approximately 40,000 patients per arm for thyroid cancer for such studies to be conducted with statistical power if typical rates of nerve paralysis are used for calculation [7,18]. Eisele [17] reports that to show a reduction of the rate of RLN injury from thyroidectomy from 2% to 1% per nerves at risk, a study group of approximately 1000 nerves would be necessary [4,10,17]; a reduction of the rate from 0.1% to 0.5% by the same statistical parameters would require evaluation of approximately 2000 nerves.

One of the recommendations in the use of IONM is to avoid contralateral lobe resection after LOS in the first lobe [9,11]. The

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Recurrent laryngeal nerve palsy in the two groups in relation to type of surgery and histology. *One patient had bilateral nerve palsy **One patient with prior unilateral nerve palsy had contralateral nerve palsy.

<table>
<thead>
<tr>
<th></th>
<th>Group A (1356 patients) n (%)</th>
<th>Group B (1009 patients) n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent nerve palsy</td>
<td>31 (2.28%)</td>
<td>28 (2.77%)</td>
<td>0.5348</td>
</tr>
<tr>
<td>Unilateral</td>
<td>29 (2.13%)</td>
<td>26 (2.57%)</td>
<td>0.5745</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2 (0.14%)</td>
<td>2 (0.19%)</td>
<td>0.8344</td>
</tr>
<tr>
<td>Transient nerve palsy</td>
<td>25 (1.84%)</td>
<td>21 (2.08%)</td>
<td>0.7923</td>
</tr>
<tr>
<td>Total Thyroidecotomy</td>
<td>16 (1.17%)</td>
<td>15 (1.48%)</td>
<td>0.6413</td>
</tr>
<tr>
<td>Completion thyroidectomy</td>
<td>4 (0.29%)</td>
<td>2** (0.19%)</td>
<td>0.9605</td>
</tr>
<tr>
<td>Total thyroidectomy + lymphectomy</td>
<td>5 (0.36%)</td>
<td>4 (0.39%)</td>
<td>0.8185</td>
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<tr>
<td>Multinodular goiter</td>
<td>10 (0.73%)</td>
<td>8 (0.79%)</td>
<td>0.9031</td>
</tr>
<tr>
<td>Differentiated carcinoma</td>
<td>8 (0.58%)</td>
<td>8** (0.79%)</td>
<td>0.7325</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>5 (0.36%)</td>
<td>3 (0.29%)</td>
<td>0.7096</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>2 (0.14%)</td>
<td>2 (0.19%)</td>
<td>0.8344</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Permanent nerve palsy</td>
<td>6 (0.44%)</td>
<td>7 (0.69%)</td>
<td>0.5917</td>
</tr>
<tr>
<td>Total Thyroidecotomy</td>
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<tr>
<td>Completion thyroidectomy</td>
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<td>0.882</td>
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<tr>
<td>Total thyroidectomy + lymphectomy</td>
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<td>1 (0.09%)</td>
<td>0.6133</td>
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<td>3 (0.22%)</td>
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<tr>
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<tr>
<td>Medullary carcinoma</td>
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</table>

reconsideration of surgical strategy after a LOS in one site must be evaluated mainly for redo surgery in patients at major risk of bilateral RLN palsy [9,19]. Following this recommendation, however, two-third of patients might require unnecessary two-stage thyroidectomy [2,9]. We don’t believe that a staged thyroidectomy can always be taken into consideration, given the fact that a LOS does not always correspond to a nerve injury and considered the risk of delaying the treatment of potentially aggressive tumors. However, given the high accuracy and the significant positive predictive value, we believe that in case of LOS, in selected cases, surgical strategy can be reconsidered.

Some authors suggest that IONM should be used only in patients at high risk of injury [10,20]. We believe that IONM could be performed routinely given that difficult cases cannot always be predicted preoperatively. Furthermore, the use of IONM in only selected cases does not allow adequate familiarity with the device and can lead to pitfalls. However, IONM can speed the surgical dissection by confirming the anticipated location and course of the nerve. Moreover, RLN paralysis occurrence diminishes the quality of life for a few weeks to months after thyroid surgery and is a major cause of medicolegal litigation [3,4,18,20,21]; for this reason we believe that any improvement in this field is welcome.

Another highlighted limit of conventional intermittent monitoring is that RLN injury is usually identified after it has occurred [9,22]. Real-time continuous intra-operative vagus monitoring can detect an impending recurrent laryngeal nerve injury with modification of the intra-operative strategy, thus avoiding nerve damage [9,22]. For this reason, we believe that the continuous monitoring represents a very interesting improvement in this field and that it can also lead to improved outcomes.

5. Conclusions

In conclusion, IONM is a safe and effective technique and it is highly predictive of the postoperative nerve function. With a strict standardization of the technique we obtained a very high sensitivity and negative predictive value, but also a good specificity and positive predictive value. For these reasons, in selected cases of patients with LOS, the surgical strategy can be reconsidered. On the other hand, this study failed to demonstrate a statistically significant decrease in the RLN paralysis rate. Further wider and multicentric studies are needed to evaluate the real benefit of this technique. Continuous monitoring could represent a very interesting improvement in this field and it could lead to improved outcomes.

Ethical approval

Ethical approval was requested and obtained from the “University of Cagliari” ethical committee.

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Author contribution

Pietro Giorgio Calò: 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.

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

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

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

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

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

Angelo Nicolosi: 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.
Conflicts of interest

All Authors have no conflict of interests.

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References


