Effectiveness of intraoperative neuromonitoring of the recurrent laryngeal nerve with intermittent vagal nerve stimulation

Marco Aurélio Vamondes Kulcsar, Felipe Toyama Aires, Danielli Matsuura, Lenine Garcia Brandão, Claudio Roberto Cernea

Abstract

Introduction: Vocal fold paralysis due to recurrent laryngeal nerve (RLN) injury during thyroidectomy occurs in 1-5% of patients, but it can reach up to 15% in reoperations. Intraoperative neuromonitoring (IONM) during thyroidectomy was first described in 1970, and has been widely used by surgeons. However, data on the IONM capacity to predict inferior laryngeal nerve function are still lacking. Objective: To evaluate the effectiveness of IONM of the RLN using intermittent stimulation of the vagus nerve during thyroidectomy to predict post-operative vocal fold function. Methods: Retrospective cohort analysis of 104 patients undergoing thyroidectomy with IONM of the RLN through intermittent vagal nerve stimulation. IONM response and vocal fold mobility were evaluated utilizing the McNemar’s test associated with the Kappa agreement coefficient. Results: The final response of RLN stimulation showed 69.23% sensitivity and 93.79% specificity (p=0.180). Conclusion: IONM of the RLN through intermittent vagal nerve stimulation during thyroidectomy is effective to predict post-operative vocal fold function.

Keywords: intraoperative neuromonitoring; laryngoscopy; thyroidectomy.
Endotracheal tube-based surface electrodes that respond to intermittent vagal nerve stimulation are the most common method used in intraoperative neuromonitoring (IONM) of the RNL because of their safety, simplicity, and applicability. Nevertheless, there are controversial data in the literature regarding their capacity to predict inferior laryngeal nerve function.

This study aimed to analyze the effectiveness of IONM of the RLN through intermittent vagal nerve stimulation to accurately predict post-operative vocal fold function.

**Methods**

**Study design and location**

This is a retrospective, descriptive, cohort study based on the analysis of patients’ records that underwent thyroidectomy with IONM of the RNL through intermittent vagal nerve stimulation in a private clinic in the city of São Paulo between January 2011 and January 2014.

The study was exempted from informed consent since there were no ethical impediments according to the Ethics Research Committee of the University of São Paulo Medical School (FMUSP) on 26 June 2014.

**Inclusion and exclusion criteria**

Patients with thyroid disease undergoing surgical treatment with IONM of the RNL through intermittent vagal nerve stimulation were included in the study. The surgical treatment criteria included suspected or confirmed malignancy diagnosis after fine-needle aspiration (FNA) biopsy, signs or symptoms of compression, substernal goiter, toxic goiter refractory to medical treatment, and esthetic complaints reported by the patient. Patients with thyroid neoplasm and/or hyperparathyroidism were excluded from the study.

**Intraoperative vagal nerve monitoring method**

Pre- and postoperative assessments of vocal fold mobility were performed. The post-operative evaluation was conducted on the 7th, 14th and 30th days. Patient vocal fold evaluation was classified accordingly to mobility:

1. Vocal fold paralysis - absence of movement;
2. Partial vocal fold immobility - partial movement;
3. Normal vocal folds.

All vocal fold mobility tests were performed by the same evaluator.

Anesthesia was induced with neuromuscular blocking agents with rapid onset of action and metabolism. Endotracheal tube-based surface electrodes connected to the NIM 3.0 system (Medtronic™) were used. Assisted mechanic ventilation along with anesthesia with propofol were maintained until the end of surgery. The endotracheal tubes were carefully selected according to the size of the patient, thus avoiding airway trauma, and the cannula electrodes were positioned at the level of the vocal folds confirmed by laryngoscopy.
Vagal nerve stimulation was performed according to a standard procedure:

1. Dissection followed by stimulation of the vagus nerve (V1);
2. Middle thyroid vein was ligated during thyroid lobe exposure;
3. Superior thyroid vessels were ligated before releasing the upper pole, always performed as close to the gland as possible in order to prevent injuries to the superior laryngeal nerve external branch;
4. Visual identification and stimulation of the RLN (R1);
5. Dissection of the RLN;
6. Branches of the inferior thyroid artery were ligated, preserving the parathyroid glands;
7. Resection of the thyroid lobe and isthmus;
8. Hemostasis during intraoperative Valsalva maneuver;
9. Final stimulation of the RLN (R2);
10. Final vagal nerve stimulation (V2).

Adopted stimulation response criteria:

A. Positive response: Final R2 and V2 stimulus with electromyographic response >100 V, increased latency up to 20% and amplitude <30% from the initial response;
B. Negative response: Final R2 and V2 stimulus with electromyographic response <100 V, or latency >20% and amplitude <30% from the initial response.

If there was no response to vagal stimulation, the cannula placement was verified, a warm saline solution was poured over the surgical area, and a new stimulation was performed after 20 min:

A. If a positive vagal nerve response was obtained, a total thyroidectomy was performed on the contralateral side following the aforementioned steps;
B. If a negative vagal nerve response was obtained, the procedure was interrupted.

**Statistical analysis**

Categorical variables were descriptively presented in tables containing absolute (n) and relative (%) frequencies. Normality of the quantitative variables was assessed using the Kolmogorov-Smirnov test. The variables were descriptively presented as median and interquartile range. The nonparametric McNemar's test associated with the Kappa agreement coefficient were applied to analyze data from IONM through intermittent vagal nerve stimulation during thyroidectomy and its correlation with post-operative vocal fold function. To this end, contingency tables were built between the times R2, V2 and laryngoscopy on the 7th postoperative day using the null hypothesis that there is no difference between the methods.
**Results**

This study analyzed a cohort of 104 patients aged 17-72 years (88, 84.6% male; 16, 15.4% female) undergoing surgical treatment for thyroid disease.

Regarding thyroid function, thyroid stimulating hormone (TSH) was normal in 99 (95.2%) cases, high in one (1%) case, and low in four (3.8%) cases. Free thyroxin values were normal in 102 (98.1%) cases and high in two patients. Antithyroid antibodies were negative in 90 (86.5%) cases.

In the sonographic evaluation, 38 (36.9%) patients had single nodules and 66 (63.1%) presented multiple nodules.

Considering the preoperative indication for surgical treatment, 58 (58.7%) patients had carcinoma, 26 (25%) presented follicular lesion, 13 had substernal goiters, two showed toxic goiters, and one patient had a nodule with benign cytopathological evaluation, but with increasing size.

Surgery extent according to intermittent IONM of the vagus nerve is described in Table 1.

There were 174 recurrent laryngeal nerves at risk: 85 on the right side and 89 on the left side. V1 and R1 showed that all nerves had a positive response in the beginning. The standard R2-V2 electromyographic responses are described in Table 2.

Laryngoscopy performed on the 7th day after surgery showed normal vocal folds in 88 (85.7%) cases, partial vocal fold immobility in 14 (13.4%) cases, and vocal fold paralysis in two (1.9%) cases. On the 14th day after surgery, 92 (88.4%) patients had normal vocal folds, 12 (11.6%) presented partial vocal fold immobility, and no patients showed vocal fold paralysis. On the 30th postoperative day, 101 (97.1%) patients had normal vocal folds, three (2.9%) showed partial vocal fold immobility, and no patients presented vocal fold paralysis.

Correlation between laryngoscopy on the 7th postoperative day and R2 and V2 is presented in Table 3 in order to assess the accuracy of the method in predicting vocal fold function.

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**Table 1. Surgery extent.**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thyroidectomy (TT)</td>
<td>58  (55.8%)</td>
</tr>
<tr>
<td>Partial thyroidectomy</td>
<td>28  (26.9%)</td>
</tr>
<tr>
<td>TT plus unilateral central neck dissection</td>
<td>5   (4.8%)</td>
</tr>
<tr>
<td>TT plus bilateral central neck dissection</td>
<td>7   (6.7%)</td>
</tr>
<tr>
<td>TT plus central and lateral neck dissection</td>
<td>1   (1%)</td>
</tr>
<tr>
<td>Completion thyroidectomy</td>
<td>3   (2.9%)</td>
</tr>
<tr>
<td>Lobectomy with central neck dissection</td>
<td>1   (1%)</td>
</tr>
<tr>
<td>Central neck dissection</td>
<td>1   (1%)</td>
</tr>
</tbody>
</table>
Thyroidectomy IONM has been standardized since 2012, leading to better and more uniform data; however, controversy regarding the effectiveness of IONM to predict RLN injury and post-operative vocal fold function still remains.

R2 showed 69.23% sensitivity and 93.79% specificity, and the results were concordant using the McNemar’s test ($p=0.180$). V2 showed sensitivity of 100.0% and specificity of 90.68%, but the results were not concordant using the McNemar’s test ($p<0.001$) (Table 4).

**Discussion**

Thyroidectomy IONM has been standardized since 2012, leading to better and more uniform data; however, controversy regarding the effectiveness of IONM to predict RLN injury and post-operative vocal fold function still remains.

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**Table 2. Electromyographic response according to side and RLN stimulation.**

<table>
<thead>
<tr>
<th></th>
<th>Pre-lobectomy</th>
<th>Post-lobectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right vagus nerve response (V)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>85 (100%)</td>
<td>77 (90.5%)</td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0%)</td>
<td>8 (9.5%)</td>
</tr>
<tr>
<td><strong>Right RLN response (R)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>85 (100%)</td>
<td>73 (85.8%)</td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0%)</td>
<td>12 (14.2%)</td>
</tr>
<tr>
<td><strong>Left RLN response (R)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>89 (100%)</td>
<td>78 (87.6%)</td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0%)</td>
<td>11 (12.4%)</td>
</tr>
<tr>
<td><strong>Left vagus nerve response (V)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>89 (100%)</td>
<td>74 (83.2%)</td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0%)</td>
<td>15 (17.8%)</td>
</tr>
</tbody>
</table>

**Table 3. Correlation between laryngoscopy on the 7th postoperative day.**

<table>
<thead>
<tr>
<th>7th postoperative day laryngoscopy</th>
<th>Normal vocal fold</th>
<th>Partial vocal fold immobility/Vocal fold paralysis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RLN response (R2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal vocal fold</td>
<td>151 (86.8%)</td>
<td>4 (2.3%)</td>
<td>155 (89.1%)</td>
</tr>
<tr>
<td>Partial vocal fold immobility/vocal cord paralysis</td>
<td>10 (5.7%)</td>
<td>9 (5.2%)</td>
<td>19 (10.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>161 (92.5%)</td>
<td>13 (7.5%)</td>
<td>174 (100%)</td>
</tr>
<tr>
<td><strong>Vagus nerve response (V2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal vocal fold</td>
<td>146 (83.9%)</td>
<td>0 (0%)</td>
<td>146 (83.9%)</td>
</tr>
<tr>
<td>Partial vocal fold immobility/Vocal fold paralysis</td>
<td>15 (8.6%)</td>
<td>13 (7.5%)</td>
<td>28 (16.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>161 (92.5%)</td>
<td>13 (7.5%)</td>
<td>174 (100%)</td>
</tr>
</tbody>
</table>
The most recent studies have shown excellent negative predictive values despite intermediate positive predictive values. Absence of response after nerve stimulation can occur not only because of nerve injury, but also as a result of apparatus malfunction, displacement of the endotracheal electrode tube and non-neural stimulation, thus making it unclear whether there was, in fact, nerve injury. Absence of response after nerve stimulation can occur not only because of nerve injury, but also as a result of apparatus malfunction, displacement of the endotracheal electrode tube and non-neural stimulation, thus making it unclear whether there was, in fact, nerve injury. Many authors have recommended interruption of the procedure after absence of response to nerve stimulation, especially in benign diseases, hence impacting on the surgeon’s decision on the surgery extent.

In the present study, a patient with papillary carcinoma underwent lobectomy, but R2 and V2 presented decreased responses. As the tumor was a T1 according to the histopathological frozen section, it was decided to interrupt the procedure. The patient presented vocal fold immobility for 45 days. Therefore, by adopting the standard care for IONM of the RLN, a possible bilateral paralysis was avoided.

Laryngoscopy on the 7th postoperative day performed in all cases showed a paresis index in 14 (13.4%) cases and paralysis in two (1.9%) cases. R2 presented sensitivity of 69.2% and specificity of 93.8%, which makes the test concordant (\(p=0.180\)). However, for V2, sensitivity (100.0%) and specificity (90.7%) were not concordant using the McNemar’s test (\(p<0.001\)). This is probably due to the false-negative cases that showed non-responses to vagal nerve stimulation, but later presented with a normal laryngoscopy on the 7th postoperative day. Descriptive analysis of the association between V2 responses of neuromonitoring and laryngoscopies showed that 6% were false-negatives.

Therefore, in order to evaluate the accuracy of the method, the Kappa coefficient was applied and showed moderate accuracy, corroborating the findings of other studies. Although the patients with false-negative responses of IONM of the RLN underwent reoperation, a possible bilateral vocal fold paralysis was completed avoided.

As shown in previous studies, IONM can change the operative management, resulting in fewer complications. Despite the small number of patients associated with low incidence of vocal fold paralysis, this study shows that IONM of the RLN with intermittent vagal nerve stimulation can accurately evaluate vocal fold function, and thus predict the post-operative function.

### Table 4. McNemar’s test.

<table>
<thead>
<tr>
<th>Statistics</th>
<th>RLN response (R2)</th>
<th>Vagus nerve response (V2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensibility</td>
<td>69.23</td>
<td>100.00</td>
</tr>
<tr>
<td>Specificity</td>
<td>93.79</td>
<td>90.68</td>
</tr>
<tr>
<td>Accuracy</td>
<td>91.95</td>
<td>91.38</td>
</tr>
<tr>
<td>Kappa coefficient</td>
<td>0.52</td>
<td>0.59</td>
</tr>
<tr>
<td>(p)-value (McNemar’s test)</td>
<td>0.180</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Due to the increasing number of thyroidectomies, this technology is of great significance in the effort to predict vocal fold function and, in some cases, even prevent the surgery.

Conclusion
Intraoperative monitoring of the vagus nerve during thyroidectomy is an effective method to predict post-operative vocal fold function.

References


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