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Intraoperative recurrent laryngeal nerve monitoring using endotracheal electromyography during parathyroidectomy for secondary hyperparathyroidism

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Abstract

Objective: To investigate the factors associated with adherence of an enlarged parathyroid gland to the recurrent laryngeal nerve (RLN) and the effectiveness of intraoperative neural monitoring (IONM).

Methods: This single-center retrospective study involved samples from 197 consecutive patients (394 RLNs; 733 parathyroid glands) who underwent parathyroidectomy and transcervical thymectomy between September 2010 and December 2014. The presence of parathyroid gland adhesion to the RLN and the clinical characteristics of patients with and without nerve adhesion were recorded. All patients underwent intraoperative monitoring of the electromyographic responses of the vocal cords using the endotracheal NIM-Response 3.0 system. The patients' postoperative clinical outcomes were recorded.

Results: Parathyroid gland adhesion to the RLN was significantly associated with maximum gland diameter (>15 mm), weight (>500 mg), and the presence of nodular hyperplasia. IONM demonstrated a sensitivity of 97.8%, specificity of 43.5%, and accuracy of 94.7% for detecting nerve damage. Parathyroid gland adhesion to 17 RLNs occurred in 3 cases (17.6%) of vocal cord

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paralysis, whereas the 377 glands without nerve adhesion resulted in vocal cord paralysis in 20 cases (5.3%).

Conclusion: Our findings demonstrated the effectiveness of IONM using endotracheal electromyography in patients who underwent parathyroidectomy for secondary hyperparathyroidism.

Keywords

Intraoperative neural monitoring, secondary hyperparathyroidism, parathyroidectomy, recurrent laryngeal nerve, paralysis, nodular hyperplasia

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Introduction

Total parathyroidectomy and transcervical thymectomy with a forearm autograft are recommended for the treatment of patients with secondary hyperparathyroidism refractory to medical treatment.[1] Complete parathyroid gland removal is essential in secondary hyperparathyroidism to prevent recurrent and persistent hyperparathyroidism.[2] Transcervical thymectomy is also essential, given that 15.5% of remnant parathyroid glands are identified in the thymus.[3,4] During the detailed exploration of the parathyroid glands, the recurrent laryngeal nerves (RLNs) are at risk of injury, with RLNs firmly adhered to the parathyroid glands at greater risk. Some studies have reported on the difficulty of removing adhered parathyroid glands after percutaneous ethanol injection therapy (PEIT).[5,6] However, there have been no detailed reports of firm parathyroid gland adhesion to RLNs not undergoing PEIT treatment during initial total parathyroidectomy for secondary hyperparathyroidism. Hemorrhage, calcification, and chronic inflammation are the typical pathological changes in large hyperplastic glands,[7] and these changes might lead to firm parathyroid gland adhesion to the RLNs. Anatomical and functional preservation of adhered RLNs is essential during the operation. Unfortunately, vocal cord paralysis after total parathyroidectomy and transcervical thymectomy has been identified.

The efficacy of intraoperative neural monitoring (IONM) during thyroid surgery has previously been reported, with excellent diagnostic capability validated for thyroid surgeries.[8–11] IONM has also been reported to have substantial utility in RLN preservation in patients requiring re-surgery or those with large goiters or invasive thyroid cancers.[12,13] The efficacy of IONM during initial total parathyroidectomy and transcervical thymectomy for secondary hyperparathyroidism is yet to be elucidated.

We aimed to investigate the characteristics of patients with parathyroid glands firmly adhered to the RLNs and the characteristics of such parathyroid glands. Additionally, we sought to determine the diagnostic validity of IONM in initial total parathyroidectomy and transcervical thymectomy for secondary hyperparathyroidism and the efficacy of IONM for the anatomical and functional preservation of the RLNs, as evaluated according to the incidence of vocal cord paralysis.

Materials and methods

Ethical review

This study was approved by the institutional review board in Nagoya Daini Red Cross Hospital (approval number: 1069) and was conducted in accordance with the guidelines published in the Declaration of Helsinki. All patients' data were retrospectively collected from their medical records and analyzed anonymously. As such, the need for informed consent was waived.

Study design

This study retrospectively investigated the characteristics of parathyroid glands firmly adhered to the RLNs. After evaluating the diagnostic validity of IONM, we evaluated operative outcomes, namely the incidence of vocal cord paralysis during surgery using IONM.

Setting and participants

Specimens were collected from surgeries performed between September 2010 and December 2014. All patients' data were obtained retrospectively from their medical records. This retrospective cohort study was performed according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

Variables

The characteristics of the patients and the parathyroid glands were evaluated. The evaluated patients' characteristics were sex, age, hemodialysis periods, preoperative serum calcium concentration, preoperative serum phosphate concentration, preoperative serum intact parathyroid hormone (PTH) concentration, and the administration of calcimimetic agents. The evaluated characteristics of the resected parathyroid glands were maximum diameter ($\geq$15 mm), weight ($\geq$500 mg), location (upper or lower gland), and histopathological change (diffuse hyperplasia or nodular hyperplasia). The diagnostic validity of IONM was calculated, and the incidence of vocal cord paralysis was investigated.

Operative indication for secondary hyperparathyroidism

Parathyroidectomy for secondary hyperparathyroidism was indicated according to the clinical practice guidelines for the management of patients undergoing chronic dialysis with secondary hyperparathyroidism.[1] However, patients with intact PTH concentrations $<$500 ng/L following treatment with calcimimetic agents also underwent parathyroidectomy, if they were unable to continue taking calcimimetic agents because of adverse events.

Preoperative evaluation

Parathyroid glands were preoperatively located by ultrasonography, computed tomography, and technetium (Tc)-99m sestamibi scanning. Patients with hoarseness and previous neck surgery were preoperatively examined by ear, nose, and throat specialists to rule out vocal cord paralysis.

IONM system

The NIM-Response 3.0 system was developed by Medtronic (Minneapolis, MN, USA) to confirm vagus and RLN preservation during thyroid and parathyroid surgeries. The NIM TriVantage EMG tube (Medtronic) is equipped with sensors for attachment to both the right and left vocal cords to identify electromyographic (EMG) responses to electronic nerve stimulation. EMG vocal cord responses can be recorded by the NIM-Response 3.0 system through the sensors of the NIM TriVantage EMG tube when the vagus nerves and RLNs are anatomically and functionally intact.

Preparations for IONM procedures

Under general anesthesia, the patients were intubated with the NIM TriVantage EMG tube to allow placement of the attached sensors on the vocal cords. Appropriate placement on the vocal cords was reconfirmed by an anesthesiologist with a fiberoptic laryngoscope after patients had been placed in a stretched neck position. The correct positioning of the NIM EMG tube was also confirmed with the NIM-Response 3.0 System before the skin incisions were made. IONM was performed according to IONM standard guidelines.[14] A small dose of non-depolarizing muscle relaxant agent was administered at intubation. Additional muscle relaxant agents were avoided to keep the EMG responses of the vocal cords precisely assessable during general anesthesia.

Definition of a negative EMG response

The current value for vagus nerve and RLN stimulation was set at 1.0 to 2.0 mA, and the latency period was set at 1.2 ms. An obtained EMG amplitude below 100 μV after electronic stimulation of the vagus nerve was defined as a negative EMG response.

Operative method

Total parathyroidectomy and transcervical thymectomy with forearm autograft were performed by four experienced surgeons at our hospital. Skin incisions were made, and the thyroid glands were exposed. Before manipulating the parathyroid glands, the vagus nerves and RLNs were identified, and EMG responses of the vocal cords to electric stimulation of these nerves were confirmed. The EMG responses were checked during the removal of each gland and the thymus, and the EMG responses were reconfirmed before skin closure. An EMG-positive response was defined as intact EMG responses identified at any point during the operation. An EMG-negative response was defined as the disappearance of EMG responses during the operation. Firm parathyroid gland adhesions to RLNs were defined as cases wherein the surgeons could not detach the RLNs from the parathyroid glands easily, and sharp dissection was required (Figure 2). Parathyroid glands without these characteristics were termed parathyroid glands not adhering to RLNs.

Postoperative diagnosis

Between postoperative days 3 and 5, the vocal cords were evaluated by ear, nose, and throat specialists using a fiberoptic laryngoscope.

Statistical analyses

The EMG responses during surgery and diagnosed vocal cord paralyses were classified into true positive (TP), true negative (TN), false positive (FP), and false negative (FN) categories. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for the diagnostic validity of IONM. Statistical analyses were performed using the independent samples *t*-test for continuous data and Fisher's exact test for the categorical variables. All statistical analyses were performed using IBM SPSS software, version 23.0 for Windows (IBM Corporation, Armonk, NY, USA). P-values <0.05 were considered significant.

Results

Participants

Between September 2010 and December 2014, 197 consecutive patients (394 RLN and 733 parathyroid gland specimens) who underwent initial total parathyroidectomy and transcervical thymectomy with forearm autograft for secondary hyperparathyroidism using IONM and who were not treated by PEIT were enrolled in the present study (Figure 1). None of the patients had hoarseness or a history of previous

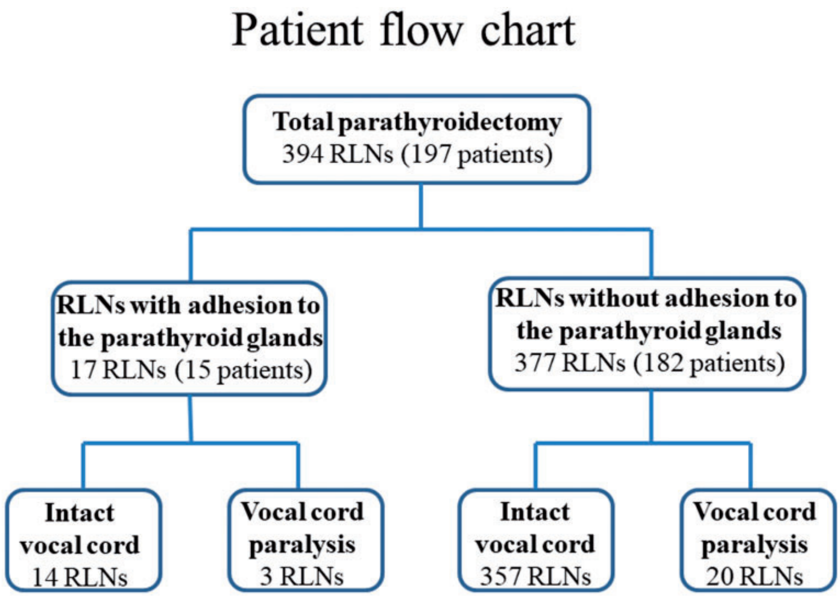

Figure 1. Flow chart showing the groupings of the patients undergoing parathyroidectomy and transcervical thymectomy.
RLN, recurrent laryngeal nerve.

neck surgery. In 197 patients (394 vagus nerves, 394 RLNs), intact EMG responses were identified following electrical stimulation of the vagus nerves and RLNs before manipulating the parathyroid glands. In 15 of the 197 patients (17/394 RLNs, 4.3%), the parathyroid glands were firmly adhered to the RLNs. Two of the 15 patients had bilateral RLN adhesions, and 13 of the 15 patients had unilateral RLN adhesions. Furthermore, 17 RLNs of the 15 patients were classified as RLNs with firm adhesion to the parathyroid glands, and, of these, 3 patients (3/17 adhered RLNs) were diagnosed with unilateral vocal cord paralysis during postoperative evaluation by ear, nose, and throat specialists. In 182 of the 197 patients, the parathyroid glands were not adhered to the RLNs. Thirteen contralateral RLNs of the 13 patients with unilateral RLN adhesion and 364 RLNs of the remaining 182 patients (total: 377 RLNs) were classified as RLNs without adhesion to the parathyroid glands. Of the 377 RLNs, 20 were associated with unilateral vocal cord paralysis (Figure 1); no bilateral vocal cord paralyses were identified. A total of 733 parathyroid glands were resected from 197 patients, with 17 parathyroid glands adhered firmly to RLNs.

Descriptive data

The characteristics of the 197 included patients were as follows: 108 men and 89 women; mean age, 55.8 ± 12.6 years; mean hemodialysis period, 4455.3 ± 4282.6 days; and mean preoperative serum intact PTH concentration, 681.8 ± 531.6 pg/mL. The characteristics of patients with and without parathyroid gland adhesions to RLNs are shown in Table 1. There was no statistically significant difference in the following patient characteristics: sex, age, hemodialysis period, preoperative serum calcium concentration, preoperative serum phosphate

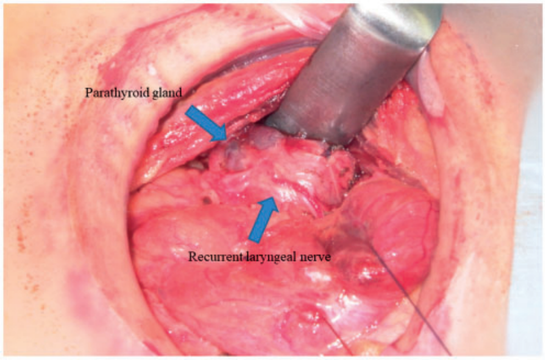

Figure 2. Parathyroid gland firmly adhered to the recurrent laryngeal nerve.

Table 1. Characteristics of the patients with parathyroid glands with and without adhesion to RLNs.

	Parathyroid glands with adhesion to RLNs 15 patients	Parathyroid glands without adhesion to RLNs 182 patients	P value	Odds ratio	95% CI	
Sex (male)	7 (46.7%)	101 (55.5%)	0.509	0.702	0.244	2.017
Age (years)	55.0 ± 11.3	56.0 ± 12.7	0.779		−5.735	7.636
Hemodialysis period (days)	4466.5 ± 3012.5	4429.9 ± 777.8	0.975		−2311.677	2238.557
Preoperative serum calcium concentration (mmol/L)	2.45 ± 0.26	2.42 ± 0.21	0.627		−0.138	0.084
Preoperative serum phosphorus concentrat-ion (mmol/L)	1.82 ± 0.34	1.87 ± 0.51	0.715		−0.217	0.316
Preoperative serum intact PTH concentration (ng/L)	740.3 ± 416.5	677.0 ± 540.6	0.659		−345.490	218.924
Preoperative administration of calcimimetics	11 (73.3%)	133 (73.1%)	0.983	1.013	0.308	3.331

RLN, recurrent laryngeal nerve; PTH, parathyroid hormone; 95% CI, 95% confidence interval.

concentration, and preoperative serum intact PTH concentration, and the administration of calcimimetic agents. Details of the parathyroid glands with and without adhesion to RLNs are shown in Table 2. Significant differences in the maximum diameter (>15 mm) ($P < 0.001$, odds ratio (OR): 5.419, 95% confidence interval (CI): 1.976–14.862), weight (>500 mg) ($P < 0.001$; OR: 6.504, 95% CI: 2.262–18.702), and histopathological change (diffuse hyperplasia or nodular hyperplasia) ($P = 0.025$; OR 2.993, 95% CI: 1.094–8.185) of the parathyroid gland were observed between the parathyroid glands with and without adhesion to the RLNs.

Table 2. Characteristics of the parathyroid glands.

	Parathyroid glands with adhesion to RLNs 17 glands	Parathyroid glands without adhesion to RLNs 716 glands	P value	Odds ratio	95% CI	
Maximum diameter >15 mm	11 (64.7%)	181 (25.3%)	<0.001	5.419	1.976	14.862
Weight >500 mg	12 (70.6%)	193 (27.0%)	<0.001	6.504	2.262	18.702
Parathyroid gland location						
Upper gland	13 (76.5%)	368 (51.4%)	0.041	3.073	0.993	9.516
Lower gland	4 (23.5%)	348 (48.6%)				
Histopathological change						
Diffuse hyperplasia	6 (35.3%)	444 (62.0%)	0.025	2.993	1.094	8.185
Nodular hyperplasia	11 (64.7%)	272 (38.0%)				

RLN, recurrent laryngeal nerve; 95% CI, 95% confidence interval.

Diagnostic validity of IONM

The results of the EMG responses intra- and postoperatively to diagnose vocal cord mobility were classified into TP, TN, FP, and FN (Table 3) categories. The related sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 97.8%, 43.5%, 97.8%, 55.6%, and 94.7%, respectively.

Impact of IONM on RLNs adhering to the parathyroid glands

Vocal cord paralyses were identified relatively more frequently, but not significantly, in RLNs with firm adhesion to the parathyroid glands (3/17 RLNs, 17.6%) than in those without adhesion (20/377 RLNs, 5.3%; Figure 3).

Discussion

In the present study, no significant differences were observed between the characteristics of the patients with and without RLN adhesion to the parathyroid glands. Hemodialysis periods, preoperative serum intact PTH concentrations, and calcimimetic agent use, despite leading to a reduction in size, were not associated with firm RLN adhesion to the parathyroid glands. The maximum diameter of >15 mm, weight of >500 mg, and nodular hyperplasia of the parathyroid gland were more frequently observed in parathyroid glands firmly adhered to RLNs. These results indicate that the existence of large parathyroid glands (>15 mm) might be associated with firm RLN adhesion to the parathyroid glands in secondary hyperparathyroidism.

Since its introduction using the NIM-Response 3.0 System, IONM has become widely used for the anatomical and functional preservation of the vagus nerves, RLNs, and the external branch of the superior laryngeal nerves.[15] There have been reports of the efficacy of IONM in thyroid surgeries.[8–10] A previous study reported an average incidence of vocal cord paralysis of approximately 4.7%, with the use of IONM.[14] IONM has also been reported to have substantial efficacy in surgery for advanced thyroid cancer and re-surgeries.[12,16,17] Although several previous studies have described the efficacy of IONM in thyroid surgeries, including parathyroid surgeries, the number of parathyroid surgeries was very small, and all of these studies evaluated primary hyperparathyroidism.[18–20] No studies exclusively

Table 3. Results of IONM.

	Intact vocal cords	Vocal cord paralysis	Total
EMG positive response	363 (true positive)	13 (false positive)	376
EMG negative response	8 (false negative)	10 (true negative)	18
Total	371	23	394

EMG positive response: intact EMG responses identified at any point during the operation.
EMG negative response: EMG responses disappeared during the operation.
IONM, intraoperative neural monitoring; EMG, electromyography.

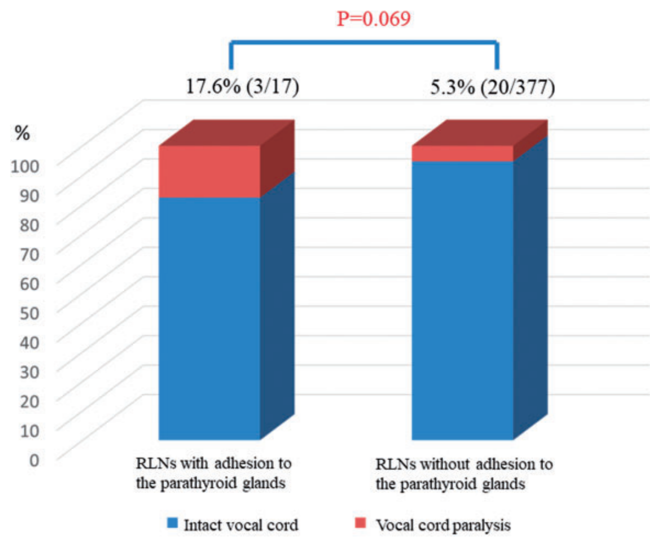

Figure 3. Frequency of vocal cord paralysis in patients with and without recurrent laryngeal nerve (RLN) adhesion to the parathyroid glands.

describing the efficacy of IONM for total parathyroidectomy and transcervical thymectomy for secondary hyperparathyroidism exist.

In this study, IONM for initial total parathyroidectomy and transcervical thymectomy for secondary hyperparathyroidism showed excellent accuracy (94.7%). However, the specificity was only 43.5%, given that there were 13 FPs and 8 FNs. According to previous reports, FPs might be caused by delayed neurapraxia owing to progressive edema and non-neural issues, such as laryngeal edema. FNs might have resulted from malpositioning of the NIM TriVantage EMG tube or temporary RLN paresis during the operation, owing to mobilization of the thyroid and parathyroid glands.[14]

In the present study, 20 (5.3%) of 377 RLNs without adhesions to the parathyroid glands were diagnosed as being associated with vocal cord paralysis even with the use of IONM. This incidence of vocal cord paralysis was similar to previously reported incidences in thyroid surgery using IONM and implies that total parathyroidectomy and transcervical thymectomy for secondary hyperparathyroidism at our hospital were performed with the same efficacy as in previous reports. However, three vocal cord paralysis (17.6%) cases were identified after detaching parathyroid glands that were firmly adhered to the RLNs. No significant difference was identified for the incidence of vocal cord paralysis between RLNs with and without firm adhesions to the parathyroid glands. This result implies that parathyroidectomy in patients with firm RLN adhesion to the parathyroid glands could be performed as safely as in patients without firm RLN adhesion, using IONM.

Staged thyroidectomy is recommended to avoid bilateral vocal cord paralysis after identifying signal loss on the first side of the neck during thyroidectomy.[21–24] Although bilateral vocal cord paralysis was not identified in this study, signal loss on the first side of the neck during parathyroidectomy can increase the risk of bilateral signal loss. This implies that staged parathyroidectomy, like staged thyroidectomy, should be considered when signal loss is identified on the first side of the neck during parathyroidectomy. Our results for the diagnostic accuracy of IONM in total parathyroidectomy and transcervical thymectomy for secondary hyperparathyroidism and the risk factors for parathyroid glands with firm adhesion to RLNs may be useful when determining the operative strategy.

One limitation of the present study is its retrospective design. Prospective studies of total parathyroidectomy and transcervical thymectomy using IONM for secondary hyperparathyroidism are expected in the future. Another limitation of this study is that the number of patients with RLN adhesions to the parathyroid glands and parathyroid glands firmly adhered to the RLNs was small. Studies with large populations are needed to validate our findings.

In conclusion, a maximum diameter of >15 mm, weight of >500 mg, and nodular hyperplasia of the parathyroid gland might be associated with adhesion of RLNs to the parathyroid glands. IONM during total parathyroidectomy and transcervical thymectomy for secondary hyperparathyroidism might enable us to perform these procedures with similar efficacy to that in previous reports of thyroid surgery with IONM. IONM also might enable us to perform safe parathyroidectomy in patients with firm RLN adhesion to the parathyroid glands.

Author contributions

TH conceived and designed the study, analyzed the data, and drafted the manuscript; TT, KF, and MO conceived and designed the study and acquired the data; TT, SN, NG, and YW interpreted the data; YT critically revised the manuscript for important intellectual content; and TI provided final approval of the version to be published.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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