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Cost-effectiveness of intraoperative neural monitoring of recurrent laryngeal nerves in thyroid lobectomy for papillary thyroid carcinoma

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Purpose: Recurrent laryngeal nerve injury after thyroid surgery may cause vocal cord palsy (VCP), which leads to unexpected additional costs. In recent years, intraoperative neural monitoring (IONM) has been used to lower the incidence rate of VCP. This study aimed to analyze postoperative management costs for patients with papillary thyroid carcinoma (PTC).
Methods: We analyzed the medical records of patients who underwent lobectomy for PTC from September 2018 to August 2019 at The Catholic University of Korea, Seoul St. Mary's Hospital. A total of 411 patients were enrolled and all the patients had voice examinations. We investigated the total costs in the IONM and non-IONM groups during a maximum 1-year follow-up and calculated the additional costs due to VCP by subtraction of the mean values in each group.
Results: The incidence rate of VCP was 3.9% (16 of 411). Extrathyroidal extension was related to VCP in Cox regression tests and accounted for 3.2% (13 of 411). VCP rate did not show a significant difference between the IONM and non-IONM groups (4.1% *vs*. 3.8%, P = 0.883). Total costs for postoperative management were higher in the IONM group than in the non-IONM group (US $328.2 ± $220.1 *vs*. $278.7 ± $141.4, P < 0.05). However, the additional costs due to VCP were significantly lower in the IONM group than in the non-IONM group ($474.1 ± $150.3 *vs*. $568.9 ± $367.6, P < 0.005).
Conclusion: The use of IONM can mitigate the increase in costs by saving additional expenses associated with VCP.
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Key Words: Cost-effectiveness analysis, Intraoperative neural monitoring, Recurrent laryngeal nerve, Thyroid cancer

INTRODUCTION

Recurrent laryngeal nerve (RLN) injury is one of the most serious complications during thyroid and parathyroid surgery. It is associated with hoarseness, dysphonia, difficulty swallowing, aspiration, and respiratory problems [1]. RLN injury may cause vocal cord palsy (VCP). Bilateral VCP is a rare but life-threatening complication. Many patients with bilateral VCP require tracheotomy. Transient VCP occurs in ranging from 0.3% to 3%, and permanent palsy in ranging from 3% to 8% [2-4]. The gold standard for preventing RLN injury is routine identification. RLN visualization is still broadly considered the standard of care [5]. However, a visualized nerve does not represent a functionally intact nerve. Patients with RLN injury go through a rehabilitation treatment, including voice therapy, in order to restore the function of the injured vocal cords. These procedures of treatment result in unexpected additional costs.

Intraoperative neural monitoring (IONM) has been proposed to help surgeons to localize the RLN and prevent injuries. IONM has been increasingly applied during thyroid and parathyroid

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surgery by surgeons in recent decades. Many studies have reported that IONM can reduce the risk of RLN injury [6,7]. Zheng et al. [8] reported that statistically significant differences were determined in terms of the incidence of transient VCP after using IONM. On the other hand, Pisanu et al. [9] showed in their meta-analysis that there was no significant difference in the incidence of RLN injury when using IONM versus visualization during thyroidectomy. The efficacy of IONM during thyroid and parathyroid surgery is still controversial.

Some studies have reported the cost-effectiveness of IONM in thyroid and parathyroid surgery. Postoperative management costs for patients with VCP should include outpatient visits, multiple laryngoscopy and video stroboscopy, voice therapy, and vocal cord medialization procedures if necessary [10]. To the best of our knowledge, few studies have evaluated the postoperative management cost in outpatient settings.

Therefore, the objective of this study was to evaluate postoperative management costs for patients who underwent lobectomy with IONM for papillary thyroid carcinoma (PTC).

METHODS

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of The Catholic University of Korea, Seoul St. Mary's Hospital (No. KC20RISI0950), which waived the requirement for informed consent due to the retrospective nature.

Patients

We retrospectively reviewed 613 patients with PTC who underwent thyroid lobectomy from September 2018 to August 2019 at The Catholic University of Korea, Seoul St. Mary's Hospital (Seoul, Korea). A total of 192 and 10 patients were excluded from analysis because of refusal of postoperative laryngoscopy and a loss of follow-up, respectively. The medical charts and pathology reports of 411 patients were reviewed and analyzed.

Preoperative workup

The preoperative work-up included physical examination, serum thyroid function test, neck ultrasonography (US), and CT. Thyroid nodules were diagnosed based on preoperative US-guided fine needle aspiration cytology. All patients who were diagnosed as PTC were evaluated by preoperative US and neck CT to confirm the size and location of tumors, presence/absence of extrathyroidal extension (ETE), lymph node status, and other abnormal findings in the neck. All patients underwent video laryngostroboscopy, perceptual voice analysis, and computerized acoustic analysis before the surgery.

Intraoperative neural monitoring procedures

General anesthesia was used for all patients with orotracheal intubation. We used a Nerve Integrity Monitor (NIM)-response 3.0 with Standard Reinforced Electromyography (EMG) endotracheal tube (Medtronic Xomed). All setup and monitoring were performed in compliance with the standard outlined in the International Neural Monitoring Study Group (INMSG) guidelines [11].

We used an intermittent nerve monitoring system. According to IONM guidelines, signals were recorded as follows: EMG amplitudes of the V1 (vagus nerve signal before surgical dissection), R1 (RLN signal at initial identification), R2 (RLN signal after thyroid removal and hemostasis), and V2 (vagus nerve signal after thyroid removal and hemostasis) [12].

Postoperative management and follow-up

All patients were regularly followed up with physical examination and thyroid function testing, every 3 months during the first year of surgery. The larynx was examined using video laryngostroboscopy (model 9200C; KayPENTAX) 2 weeks after surgery. Video-stroboscopic examination was performed to identify the following findings: vocal fold edema, subglottic edema, symmetry of arytenoids and vocal folds, vocal fold regularity, and presence of muscle tension dysphonia. When VCP was identified, vocal function exercise was performed for 6 weeks. After vocal function exercise, indirect voice therapy was applied for 1 month to improve the condition of the larynx in the patients who did not show restoration of VCP. Vocal function exercise was then performed again in these patients for 6 weeks, and video-stroboscopic examinations were repeated.

Cost analysis

The total costs were calculated by the summation of outpatient costs and examination costs for a maximum of 1 year after surgery. Outpatient costs were incurred from the otolaryngology clinic, not from the endocrine surgery clinic, because it did not make a difference between the IONM and non-IONM groups. For the same reason, admission and operation costs were not included as well. Examination costs included video laryngostroboscopy, vocal function exercise, and indirect voice therapy.

Statistical analysis

Continuous variables were presented as means with standard deviations, and categorical variables as numbers with percentages. The Student t-test and the Pearson chi-square test or the Fisher exact test were used to compare continuous and categorical variables, respectively. Univariate and multivariate Cox regression analyses were performed to identify the predictors of VCP, and hazard ratios (HRs) with 95% confidence

intervals (CIs) were calculated. All statistical analyses were performed using the IBM SPSS Statistics ver. 24.0 (IBM Corp.).

RESULTS

Baseline clinicopathologic characteristics

Table 1 shows the baseline clinicopathologic features of 411 enrolled patients who underwent lobectomy with IONM for PTC. The mean age was 45.3 years (range, 21–80 years). A total of 25.8% of patients were male and 74.2% were female. Tumor size ranged from 0.2 to 5.5 cm and the mean value was 1.0 cm. Of the total enrolled patients, 13 had ETE (13.2%) and 16 had VCP (3.9%). With regard to pathologic findings, about 90% were confirmed to be early-stage PTC in size (Table 1). Three hundred and sixty-six patients were pathologically classified into the T1 category (89.1%), 25 patients pT2 (6.1%), and 20 patients pT3a or pT3b (4.9%). A total of 42.6% was node-positive (n = 175).

Comparison of baseline clinicopathologic features between the IONM and non-IONM groups and clinical factors relevant to vocal cord palsy after lobectomy

We compared age, sex, tumor size, ETE, number of harvested and positive lymph nodes, and pathologic stage between the IONM and non-IONM groups. The tumor size in the IONM group was significantly larger than in the non-IONM group (1.3 ± 0.9 *vs.* 0.8 ± 0.6, P < 0.001). In line with that, the pathologic T category also showed a significant association with the IONM use (P < 0.001). While less than 80% of patients were T1 category in the IONM group (115 of 147, 78.2%), the majority of patients in the non-IONM group were pathologically confirmed T1 category (251 of 264, 95.1%). In terms of, sex, the number of harvested and positive lymph nodes, pathologic N category, TNM stage, and ETE, our data showed no significant difference between the IONM and non-IONM groups. In particular, the VCP rate resulted in no significant difference depending on IONM use (4.1% *vs.* 3.8%, P = 0.883) (Table 2).

We also analyzed clinical parameters that influence VCP after lobectomy. ETE was significantly associated with VCP after lobectomy according to univariate and multivariate Cox regression analysis (HR, 14.296; 95% CI, 3.856–53.008; P < 0.001). Meanwhile, there was no statistical significance between tumor size and VCP in multivariate analysis (Table 3).

Total follow-up cost analysis after lobectomy

In Table 4, we compared outpatient costs after surgery between the IONM and non-IONM groups. The total costs were higher in the IONM group compared to the non-IONM

Table 1. Baseline clinicopathologic characteristics

Characteristic	Data
No. of patients	411
Age (yr)	45.3 ± 12.8 (21–80)
Sex, male:female	1:2.9
Male	106 (25.8)
Female	305 (74.2)
Tumor size (cm)	1.0 ± 0.8 (0.2–5.5)
ETE	13 (3.2)
Harvested LNs	6.5 ± 4.5 (1–24)
Positive LNs	1.2 ± 1.9 (0–10)
T category	
pT1	366 (89.1)
pT2	25 (6.1)
pT3a	7 (1.7)
pT3b	13 (3.2)
N category	
pN0	236 (57.4)
pN1a	175 (42.6)
TNM stage	
I	375 (91.2)
II	36 (8.8)
Vocal cord palsy	16 (3.9)

Values are presented as number only, mean ± standard deviation (range), or number (%).
ETE, extrathyroidal extension; LN, lymph node.

Table 2. Baseline clinicopathologic characteristics in the IONM group *vs.* non-IONM group

Characteristic	IONM group (n = 147)	Non-IONM group (n = 264)	P-value
Age (yr)	45.1 ± 13.6	45.4 ± 12.4	0.817
Sex			0.061
Male	46 (31.3)	60 (22.7)	
Female	101 (68.7)	204 (77.3)	
Tumor size (cm)	1.3 ± 0.9	0.8 ± 0.6	<0.001*
ETE	7 (4.8)	6 (2.3)	0.238
Harvested LNs	6.6 ± 4.7	6.4 ± 4.5	0.723
Positive LNs	1.4 ± 2.0	1.1 ± 1.9	0.208
T category			<0.001*
pT1	115 (78.2)	251 (95.1)	
pT2	21 (14.3)	4 (1.5)	
pT3a	4 (2.7)	3 (1.1)	
pT3b	7 (4.8)	6 (2.3)	
N category			0.145
pN0	77 (52.4)	159 (60.2)	
pN1a	70 (47.6)	105 (39.8)	
TNM stage			0.717
I	133 (90.5)	242 (91.7)	
II	14 (9.5)	22 (8.3)	
Vocal cord palsy	6 (4.1)	10 (3.8)	0.883

Values are presented as mean ± standard deviation or number (%).
IONM, intraoperative neuromonitoring; ETE, extrathyroidal extension; LN, lymph node.
*P < 0.05, statistically significant.

Table 3. Univariate and multivariate analyses of clinical parameters associated with vocal cord palsy

Parameter	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Tumor size	1.539 (1.001–2.367)	0.050		
ETE	14.296 (3.856–53.008)	<0.001*	14.296 (3.856–53.008)	<0.001*

HR, hazard ratio; CI, confidence interval; ETE, extrathyroidal extension.
*P < 0.05, statistically significant.

Table 4. Costs for postoperative management according to the incidence of VCP

Variable	Cost (US dollars)		P-value
	IONM group (n = 147)	Non-IONM group (n = 264)	
Total	328.2 ± 220.1	278.7 ± 141.4	0.006*
VCP (–)	297.0 ± 145.4	263.9 ± 103.1	0.009*
VCP (+)	771.1 ± 295.7	832.8 ± 470.7	0.078
Cost gap	474.1 ± 150.3	568.9 ± 367.6	0.006*

Values are presented mean ± standard deviation.
VCP, vocal cord palsy; IONM, intraoperative neuromonitoring.
*P < 0.05, statistically significant.

group (US $328.2 ± $220.1 *vs.* $278.7 ± $141.4, P = 0.006). For patients 'without' postoperative VCP, the sum of costs in the IONM group was higher ($297.0 ± $145.4 *vs.* $263.9 ± $103.1, P = 0.009). In contrast, follow-up costs did not show a statistical difference depending on the use of IONM for patients 'with' VCP (P = 0.078). The additional costs due to VCP in the IONM group were significantly lower than in the non-IONM group ($474.1 ± $150.3 *vs.* $568.9 ± $367.6, P = 0.006).

DISCUSSION

The IONM system mainly consists of a nerve stimulator, an EMG-attached endotracheal tube, and a monitor that visualizes detected electrical signals. The movement of vocal cord muscles after nerve stimulation is transformed into graphs and figures on the monitor [13]. VCP after thyroid surgery is mainly attributable to RLN injury, which is a major concern in terms of thyroidectomy. It is known that VCP occurs in 3%–5% of patients after thyroidectomy [14]. Patients with VCP may suffer from permanent speech, swallowing dysfunction, or even airway obstruction in case of bilateral VCP. Therefore, IONM use in thyroid surgery has steadily increased over the past decades [15].

According to a survey by Feng et al. [15], 83% of surgeons in charge of thyroidectomy responded using IONM. Nevertheless, the efficacy of IONM use is debatable. Bai and colleagues reviewed 34 studies in their meta-analysis, which found a significant decrease in total, transient, and permanent RLN injury [16]. Snyder et al. [17] reported routine IONM use during thyroidectomy significantly reduced RLN injury. Demiryas et al. [18] retrospectively reviewed a total of 191 patients and the result showed a significantly lower rate of VCP in the group with IONM usage. On the other hand, Cirocchi et al. [19] reported, in a meta-analysis result from 5 randomized controlled trials with 1,558 patients, that it is difficult to discuss the superiority or inferiority of IONM over visualization. Brajcich and McHenry [20] analyzed a total of 627 patients who underwent thyroidectomy and IONM use showed no impact on the rate of permanent RLN injury during thyroidectomy. In short, evidence is still lacking as to whether IONM actually influences the rate of RLN injury or VCP.

Several studies have investigated the incidence of VCP. Misiolek et al. [21] analyzed 466 patients who underwent thyroid operation due to cancer and the rate of postoperative VCP was 4.7%. Staubitz et al. [22] reported in their multicenter study that postoperative VCP was diagnosed in 50 of the 4,598 patients (1.1%), with IONM used in 4,182 patients (91.0%) and IONM was associated with a lower risk of VCP in multivariate analysis. Yu et al. [23] investigated 344 patients who underwent high-risk thyroid surgery and reported that the VCP rate was 1.9% with IONM used for all the enrolled patients. In our retrospective data, the incidence rate of VCP was 3.9%, which was in line with previous studies. We also investigated whether VCP depended on IONM use. Despite the pathologic feature of the IONM group being more aggressive than that of the non-IONM group, there was no significant difference between each group with regard to VCP rate. In our analysis, we found that the IONM group included a more aggressive pathologic T category

and a relatively large tumor size. Therefore, if we assume that both groups constituted the same pathologic category, IONM would lower the VCP incidence. A randomized controlled trial with prospective data will need to be performed to verify this hypothesis.

We investigated 411 patients who underwent lobectomy for PTC and showed the cost-effectiveness of IONM by analyzing those additional costs due to VCP in the IONM and non-IONM groups, respectively. The result was in line with some studies in the past. Wang et al. [24] reported in a stimulated-based study that IONM was cost-effective if the rate of VCP was 33.6% at 1 month, 22.9% at 2 months, 9.8% at 6 months, and 3.8% at 12 months. Rocke et al. [25] postulated visual selective IONM was the most cost-effective approach when its RLN injury rate dropped below 1.9%. Al-Qurayshi et al. [26] verified using the Markov chain model that IONM was cost-effective in patients undergoing bilateral thyroid surgery. On the other hand, Gremillion et al. [27] reported that the use of IONM increased the cost of each surgery by $387 and did not reduce the number of injured nerves. IONM cost per procedure was not taken into consideration in our cost analysis. Considering that cost per IONM procedure has nothing to do with the follow-up period, the additional costs due to VCP will have little effect on the total management cost, as the follow-up period gets longer. In the near future, we have a plan to perform a prospective analysis to verify that longer follow-up will offset the cost per procedure.

Meanwhile, IONM use has some drawbacks. Firstly, it takes additional costs. In South Korea, we have criteria to meet for getting coverage from national health insurance, such as huge goiter over 4 cm in maximal diameter, pathologically confirmed central neck node metastasis, previous unilateral VCP, or thyroid capsular invasion, especially posterior. Except for high-risk patients like that, surgeons and patients are reluctant to use IONM with higher costs including IONM cost per procedure. Secondly, IONM has a low positive predictive value (PPV). PPV refers to the probability that subjects with loss of signal at the completion of surgery will have vocal cord dysfunction postoperatively, according to INMSG guideline 2018 from the laryngoscope [28]. Wang et al. [24] conducted a prospective study with 500 total thyroidectomy patients using NIM 3.0 response equipment and PPV was 77.4%. That means, even if there was no nerve injury (negative), IONM gives no signals for about 1/4 of the patients. Thirdly, it is associated with muscle relaxants used for general anesthesia [29]. Vecuronium bromide is commonly used for the convenience of tracheal intubation. EMG signal is highly affected by how long and how much muscle relaxant is administered before nerve stimulation. Even, there has been no recommendation on the way muscle relaxant is used. Lu et al. [30] presented the use of neuromuscular blocking agents during thyroid surgery to restore neuromuscular function and allow the IONM system more effective.

In South Korea's health insurance service system, patients pay part of the medical cost to the institution and the insurance corporation cover the rest of the cost, but it goes not to patients, but directly to the institutions. We also have the Health Insurance Review and Assessment Service (HIRA) to prevent over-treatment and it monitors whether an institution provides patients with appropriate services or not. When a doctor does not follow the guidelines or indications, the insurance corporation may not pay the rest of the cost. We have such a highly monitored and checked medical system that thyroid surgeons tend to use IONM for only patients with a high risk that HIRA could admit. That is the reason why a smaller number of patients were enrolled in the IONM group compared to the non-IONM group.

This study has some limitations. It is a retrospective analysis in nature. Because patients were not randomly assigned, both groups showed much different baseline characteristics, such as even the number of patients and aggressiveness of PTC. Therefore, It is difficult to simply compare the total costs between 2 groups with different sizes. We overcame that statistical weakness by calculating additional costs for each group, and there was a statistical difference between the IONM and non-IONM groups ($P = 0.006$). In fact, the cost patients paid for the IONM procedure itself was $230 per operation. If the IONM cost per procedure had been considered as additional costs, the total additional costs of the IONM group would have overtaken that of the non-IONM group ($704.1 ± $150.3 *vs.* $568.9 ± $367.6). However, from a long-term perspective, VCP can affect one's quality of life and even economic status, not for a maximum of 1 year but years even for the rest of the patient's lifetime. Despite we did not take the procedure cost of IONM into account in this study, we hypothesize total additional costs of the IONM group will not surpass that of the non-IONM group in a long-term follow-up study, which we plan to conduct in the near future.

Few studies have been conducted on the cost-effectiveness of IONM in thyroid surgery. Rocke et al. [25] conducted a study in the setting of total thyroidectomy and found that visual identification alone is more cost-effective than IONM for most surgeons. Wang et al. [24] defined an average simulated model as a 40-year-old female patient who underwent total thyroidectomy and concluded IONM is cost-effective for permanent RLN injuries. Al-Qurayshi et al. [26] investigated the cost-effectiveness of IONM in preventing bilateral RLN injury. Our study showed for the first time that IONM is also cost-effective for patients with less aggressive PTC who just need thyroid lobectomy. More relevant studies on the cost-effectiveness of IONM in thyroid surgery need to be conducted in the future.

It is difficult to affirm that IONM reduces the prevalence of postoperative VCP. However, IONM use for patients with early staged PTC, at least, is a cost-effective option, considering that voice dysfunction may lower patients' quality of life and increase the economic burden.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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