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Original Article

Application of intraoperative nerve monitoring for recurrent laryngeal nerves in minimally invasive McKeown esophagectomy

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SUMMARY. **Background: Mediastinal lymphadenectomy is of great importance during esophagectomy for esophageal squamous cell carcinoma. However, recurrent laryngeal nerve (RLN) injury is a severe complication caused by lymphadenectomy along the RLN. Intraoperative nerve monitoring (IONM) can effectively identify the RLN and reduce the incidence of postoperative vocal cord paralysis (VCP). Here, we describe the feasibility and effectiveness of IONM in minimally invasive McKeown esophagectomy. Methods: A total of 150 patients who underwent minimally invasive McKeown esophagectomy from 2016 to 2020 were enrolled in this study. We divided the patients into two groups: a neuromonitoring group (IONM, $n = 70$) and a control group (control, $n = 80$). Clinical data, surgical variables, and postoperative complications were retrospectively analyzed and compared. Results: There was no significant difference in baseline data between the two groups. Postoperative VCP occurred in six cases (8.6%) in the IONM group, which was lower than that in the control group (21.3%, $P = 0.032$). Postoperative pulmonary complications were found in five cases (7.1%) and 14 in the control group (18.8%, $P = 0.037$). The postoperative hospital stay in the IONM group was significantly shorter than that in the control group (8 vs. 12, median, $P < 0.001$). The number of RLN lymph nodes harvested in the IONM group was higher than that in the control group (13.74 ± 5.77 vs. 11.03 ± 5.78, $P = 0.005$). The sensitivity and specificity of IONM monitoring VCP were 83.8% and 100%, respectively. A total of 66.7% of patients with a reduction in signal showed transient VCP, whereas 100% with a loss of signal showed permanent VCP. Conclusion: IONM is feasible in minimally invasive McKeown esophagectomy. It showed advantages for distinguishing RLN and achieving thorough mediastinal lymphadenectomy with less RLN injury. Abnormal IONM signals can provide an accurate prediction of postoperative VCP incidence.**

KEY WORDS: **esophagus, intraoperative nerve monitoring, McKeown esophagectomy, recurrent laryngeal nerve.**

Esophageal cancer is highly malignant and lethal. Adenocarcinoma is the main pathological type in Western countries, whereas in China, more than 90% of patients with esophageal cancer have squamous cell carcinoma.[1] Depending on the extent of lymphadenectomy, the incidence of recurrent laryngeal nerve (RLN) injury after esophagectomy is between 1% and 45.3%.[2,3] Lymphadenectomy along the RLN may cause injury to the nerve. The RLN innervates the intrinsic laryngeal muscles, thereby regulating the coordinated movements of the vocal cords.[4] RLN injury often results in vocal cord paralysis (VCP), causing hoarseness, aspiration, pneumonia, and sometimes life-threatening conditions. VCP after surgery is a considerable complication after esophagectomy. Therefore, during esophagectomy, clinicians focus on protecting the RLN and achieving thorough mediastinal lymphadenectomy with less RLN injury.

Intraoperative nerve monitoring (IONM) has been widely used in thyroid and parathyroid surgery to help identify the RLN and reduce RLN injury. In recent years, IONM has also been applied in mediastinal lymphadenectomy in esophagectomy and found to

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improve the efficiency of mediastinal lymphadenectomy and reduce RLN injury.[3,5] However, these studies have shortcomings such as small sample sizes and nonstandard operation methods. In this study, we retrospectively analyzed patients who underwent minimally invasive McKeown esophagectomy and 2-field lymphadenectomy utilizing IONM and evaluated the feasibility and efficacy of this procedure in Peking Union Medical College Hospital.

MATERIALS AND METHODS

From 2016 to 2020, a total of 150 patients who underwent minimally invasive McKeown esophagectomy and 2-field lymphadenectomy at Peking Union Medical College Hospital were included in the study. All patients were diagnosed with esophageal squamous cell carcinoma by gastroscopic biopsy, and the tumor location was confirmed by upper gastrointestinal angiography and enhanced computed tomography examination. Positron emission tomography (PET) and enhanced magnetic resonance imaging (MRI) of the head were used to exclude distant metastases. All patients were examined by laryngoscopy to confirm intact vocal cords before the operation. According to the IONM utilization status, patients were divided into the IONM group (September 2018 to December 2020, $N = 70$), and the control group (January 2016 to August 2018, $N = 80$). The study was approved by the independent medical ethical committee of the Peking Union Medical College Hospital, and informed consent was obtained from all participants.

IONM technique

IONM is widely used in open and endoscopic thyroid surgery at Peking Union Medical College Hospital. Patients in the IONM group were intubated with Medtronic Nerve Integrity Monitor (NIM) TriVantage® Electromyography (EMG) endotracheal tubes (Jacksonville, FL, USA). The exploratory electrodes above the cuff was confirmed to adhere to the vocal cord by laryngoscopy. Patients underwent IONM by the NIM-response® system 3.0 (Medtronic Inc., Jacksonville, FL, USA). A NIM-eclipse® bipolar stimulator probe (Medtronic Inc.) and a 1 mA stimulus current was used to identify the RLN and obtain an electromyogram (EMG) waveform from the NIM-Response system. No muscle relaxants and sevoflurane were used during thoracic phase surgery.

Anesthesia and surgical methods

General anesthesia was administered to all patients. After the induction of anesthesia, traditional single-lumen endotracheal tubes or IONM endotracheal tubes were inserted. A bronchial blocker was inserted into the right main bronchus under the guidance of a fiber bronchoscope. The patient was arranged in a left semiprone position, and artificial pneumothorax was created by 8 mm Hg of CO_2 insufflation pressure. In thoracic phase surgery, the esophagus was mobilized, and the azygos vein was ligated with Hem-o-lok and dissected. First, we made an incision of the dorsal and ventral pleura of the upper esophagus and dissected lymph nodes around the right RLN. At the cross-point of the right vagal nerve and subclavian artery, we used IONM to detect the right RLN and obtained EMG waveform amplitude R1 before dissection (Fig. 1A). After dissection of the lymph nodes around the right RLN, we detected the right RLN again and obtained EMG waveform amplitude R2 (Fig. 1B). Afterwards, the esophagus was drawn up, and lymph nodes around the left RLN were dissected. The same method was used to obtain the EMG waveform amplitudes L1 and L2 (before and after the dissection; Fig. 1C and D). The esophagus was resected en bloc with the surrounding mediastinal lymph nodes. Then, the patient was turned to the supine position, laparoscopic phase and cervical anastomosis were performed. All patients were admitted to the intensive care unit for a minimum of one night of observation after the operation.

Evaluation of the study

The baseline information of all the patients, including sex, age, tumor location, neoadjuvant treatment status, and other clinical data, was collected from the medical record database in the hospital. A decreasing EMG waveform amplitude of more than 50% (R2/R1 or L2/L1 $< 50\%$) after dissection of lymph nodes around the RLN was considered a reduction in the signal (ROS). Failure to detect R2 and L2 (EMG waveform amplitude = 0) was considered loss of signal (LOS). ROS and LOS were considered IONM abnormality. Laryngoscopy was performed in all patients to evaluate vocal cord function 7 days after the operation, and vocal cord movement disorder was considered to be a positive VCP. Evaluation of postoperative complications included anastomotic leakage, respiratory system complications, cardiac system complications, and 30-day mortality. Postoperative pathological TNM stage was evaluated according to the 2015 Union for International Cancer Control guidelines. All patients were followed up for at least 1 year. The follow-up information of all patients was updated by telephone and questionnaire letters every 3 months. Patients with recurrent VCP were evaluated for clinical symptoms every 3 months, and the laryngoscope was reviewed 6 months after the operation. Transient VCP was considered with the recovery of vocal cord movement and permanent VCP without recovery 6 months later.

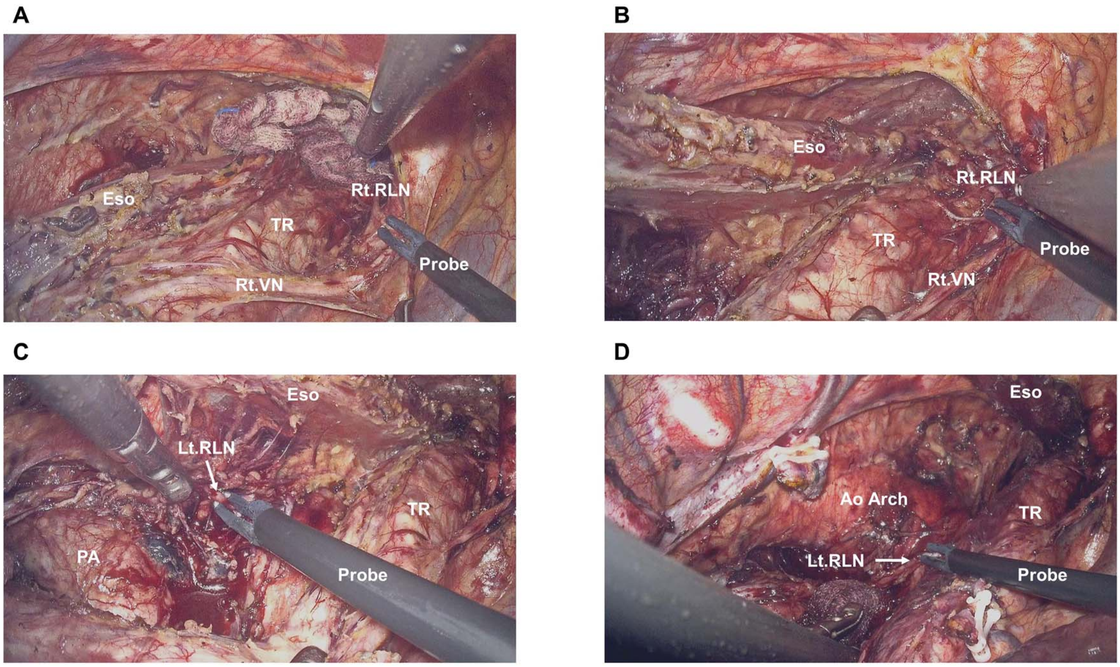

Fig. 1 IONM detection of RLN. A. We use IONM to detect the right RLN and obtain EMG waveform amplitude R1 before visualization. B. We detected the right RLN again and obtained EMG waveform amplitude R2 after dissection. C. We detected the left RLN and obtained EMG waveform amplitude L1 before visualization. D. We detected the left RLN and obtained EMG waveform amplitude L2 after dissection. VN, vagus nerve; RLN, recurrent laryngeal nerve; Eso, esophagus; TR, trachea; Probe, stimulator probe; PA pulmonary artery; Ao Arcgh, arotic arch

Statistical method

Analysis was performed using Statistical Product and Service Solutions 22.0 statistical software. The measurement data are expressed as the means ($x \pm s$) or medians (P25, P75). Student's t-test or nonparametric test was selected to compare the continuous variables between groups according to the normal distribution test (K–S test). The chi-squared test was used to compare frequencies of the categorical variables. $P < 0.05$ was considered to indicate significant differences.

RESULTS

Two cases with no EMG waveform amplitude R1 and L1 which may be caused by mechanical problem were excluded to avoid false positive situation. The baseline patient characteristics are shown in Table 1. There were no differences between the two groups in sex, age, tumor location, postoperative pathological stage, or preoperative treatment. The surgical and postoperative characteristics are shown in Table 2. There were no significant differences between the two groups in thoracic phase operation time or estimated blood loss. The IONM group obtained more RLN lymph nodes than the control group (13.74 ± 5.77 vs. 11.03 ± 5.78, $P = 0.005$). The postoperative VCP rate in the IONM group was significantly lower than that in the control group (8.6% vs. 21.3%, $P = 0.032$). Meanwhile, the percentage of respiratory complications was lower in the IONM group (7.1% vs. 18.8%, $P = 0.037$). There was no significant difference in the rates of complications such as anastomotic leakage, cardiovascular complications, or 30-day mortality between the two groups. As a result, the postoperative hospital stay in the IONM group was significantly shortened (8 vs. 12, median, $P < 0.001$).

In the IONM group, we were able to detect the RLN before visualization. There were three cases of ROS, of which 100% (3/3) had VCP and 66.7% (2/3) returned to normal 6 months later. There were two cases of LOS, of which 100% had VCP, and none of them had returned to normal after 6 months. Thus, the negative predictive value (NPV, the signal was normal, and the vocal cords were normal) was 98.5% (64/65). Positive predictive value (PPV, signal damage and abnormal vocal cords) was 100% (5/5). The sensitivity and specificity were 83.3% (5/6) and 100% (64/64), respectively (Table 3).

DISCUSSION

The extent of mediastinal lymphadenectomy in esophageal cancer is still under debate.[6] Three-field lymphadenectomy is not recommended in many institutes because of its inability to reduce cervical lymph node recurrence, resulting in increased morbidity.[7] However, Law and Wong suggested that esophageal cancer is prone to metastasis to the bilateral RLN lymphatic chains, with a positive metastasis rate as high as 18%–43.4%.[8] Studies have also shown that

Table 1 Baseline characteristics

Variables	IONM group ($N = 70$)	Control group ($N = 80$)	P value
Age (years)	62.99 ± 8.81	61.96 ± 7.12	0.433
Sex			0.571
Male	59	70	
Female	11	10	
Tumor location			0.927
Upper	5	6	
Middle	45	49	
Lower	20	25	
Neoadjuvant therapy			
No	45	57	0.615
Chemotherapy	22	21	
Chemotherapy + Radiotherapy	3	2	
Postoperative staging			0.456
I	25	27	
II	18	16	
III	22	34	
IVA	5	3	
Concomitant disease			
Hypertension	20	22	0.885
Diabetes mellitus	9	12	0.706
Cardiovascular disease	8	8	0.777
Respiratory disease	13	15	0.977

Table 2 Surgical and postoperative characteristics

Variables	IONM group	Control group	P value
Postoperative hospital stay (days)	8(7,9)	12(11,15)	<0.001
Total operation time (minutes)	314.36 ± 70.10	309.06 ± 66.49	0.636
Estimated blood loss (mL)	100(100,200)	100(100,200)	0.933
Intraoperative blood transfusion	3	2	0.544
Conversion to thoracotomy	1	1	0.924
Lymph node harvest			
Left RLN	9.90 ± 5.26	6.69 ± 4.51	<0.001
Right RLN	3.84 ± 2.03	4.33 ± 2.96	0.240
Total RLN	13.74 ± 5.77	11.03 ± 5.78	0.005
Total thoracic	28.69 ± 9.23	25.03 ± 10.32	0.024
Postoperative complications			
VCP	6(8.6%)	17(21.3%)	0.032
Anastomosis leak	7(10%)	9(11.3%)	0.805
Respiratory complications	5(7.1%)	15(18.8%)	0.037
Cardiovascular complications	3(4.3%)	3(3.8%)	0.867
Chylothorax	1(1.4%)	2(2.5%)	0.640
Postoperative mortality	1(1.4%)	1(1.4%)	0.924

Table 3 Results of IONM

	Evaluation with IONM		
	LOS	ROS	–
Motion of vocal cord (POD7)			
+	2	3	1
–	0	0	64

POD, postoperative day.
+, means loss of motion of vocal cord checked by laryngoscopy.
-, means no signs of paralysis checked by laryngoscopy or adequate response on IONM.

thorough mediastinal lymphadenectomy around the RLN contributes to a significantly higher 5-year survival rate.[9] Malassagne *et al*. also pointed out that lymph node metastases to the RLN are an important independent risk factor for poor prognosis.[10] In this study, we utilized IONM to help identify RLNs and reduce RLN injury and the incidence of postoperative VCP. Furthermore, the number of lymph nodes dissected around the RLN in the IONM group was significantly higher than that in the control group. Therefore, thorough mediastinal lymphadenectomy plays an important role in esophagectomy and accurate pathological staging of patients, which may confer survival benefits.

The IONM equipment includes a recording terminal, a stimulation probe and an EMG monitor. A single-lumen endotracheal tube with exploratory electrodes above the cuff is routinely used to receive the signal. During IONM, electric current is generated from the stimulation probe to stimulate the RLN, and nerve impulses are generated to contract the intrinsic muscles (criciothyroid muscles) to generate EMG signals. The resulting EMG waveform is displayed on the EMG monitor. In esophageal surgery, some studies have confirmed that IONM can significantly reduce the postoperative VCP rate (open surgery 9.8%–0%, minimally invasive surgery 32.1%–9.7%).[3,5] Zhong *et al.* reported 54 cases of esophagectomy utilizing IONM to reduce the incidence of RLN paralysis and postoperative pneumonia. However, the surgeons used a left thoracotomy approach, which is not the standard surgical approach currently, so the upper mediastinal lymph nodes could not be thoroughly dissected.[3] In 2018, Kobayashihong *et al.* compared 31 cases with IONM with 56 cases with non-IONM. They also found that the incidence of VCP in the IONM group was significantly lower with fewer incidences of postoperative aspirations and shorter hospital stays.[5] In 2020, IONM was used in robot-assisted Ivor Lewis esophagectomy and achieved good results. However, the study only enrolled 10 patients.[11] This study is currently the largest sample size of IONM utilizing research in the literature.

RLN injury results in VCP, which may increase the risk of aspiration, pneumonia, gastrostomy/tracheostomy, and rehospitalization.[12] Many factors affect the incidence of VCP after esophagectomy. The left RLN is located in the narrow space adjacent to the bronchus and arises a long course from the aortic arch. The anatomical relationship around the left RLN is complicated with the aortic arch, main pulmonary artery, left main bronchus, and thoracic duct with abundant blood supply. Therefore, the left RLN was the predominant location of RLN injury.[13] Moreover, multivariate analysis suggests that long-term surgery and advanced patient age are independent risk factors for VCP during esophagectomy.[2]

We suggest that IONM has the following three advantages. First, IONM can help us to distinguish the RLN before visualization, especially in some neoadjuvant therapy patients with complicated anatomical statuses. We can identify the RLN before touching, avoiding direct injury to the RLN when dissecting the lymph nodes around the nerve. Furthermore, small branches may be found and preserved from the RLN. Without IONM, even if there is no obvious RLN injury, these branches may be damaged, leading to postoperative VCP.

Second, IONM may help in postoperative VCP prognosis according to the EMG signal. It is generally believed that during IONM, a decreasing EMG waveform amplitude of more than 50% or delay of latency are considered RLN injuries.[14] Animal experiments showed that a decrease in EMG amplitude is more meaningful than a delay in latency in predicting RLN injury. This study showed that in the IONM group, 65 patients had intraoperative EMG amplitudes decreasing less than 50%, and no VCP was found after the operation. A total of 66.7% of ROS showed transient VCP after the operation, which recovered within half a year. One hundred percent of LOS patients were found to have permanent VCP. Therefore, the IONM results may provide an accurate prediction of postoperative VCP incidence in patients.

Third, IONM can help surgeons improve surgical manipulations. The mechanism of RLN injury includes traction injury, electric heating injury, compression injury, clamp injury, ligation injury, transverse injury, and so on. Among them, transverse injury is the most serious, whereas traction injury is the lightest and has the fastest recovery. For traction injuries, the EMG signal may be restored during the operation, whereas electric thermal injury, clamp injury, and transection injury will immediately lose part or all of the signal, and it cannot be recovered. For instance, patients with RLN injury mainly had early cases of IONM (data not shown). We found that the use of energy devices when dissecting RLN lymph nodes, especially ultrasonic knives, may cause RLN injury. Therefore, we improved our surgical manipulation by blunt division and bipolar electrocoagulation when dissecting RLN lymph nodes, which can significantly prevent RLN injury.

The diagnostic accuracy of IONM is a major limitation of this technology. Since IONM was used to diagnose RLN injury in the 1970s, many studies have shown that the NPV is high (92%–100%), but the PPV of IONM is relatively low and variable (10%–90%) in thyroid surgery.[15] False positive signals (signal loss of complete vocal cord activity) are prone to appear during surgery. This problem can be improved through standardized IONM application guidelines. Recording terminal disconnections, such as tracheal intubation dislocation, may cause false positive signals. We use video laryngoscope during intubation to confirm that the electrode piece is in good contact with the vocal cord. We also use fiberoptic bronchoscopy to help adjusting the tube position in case of tube dislocation during surgery. Stimulation side problems such as probe malfunction, blood or fascia covering the stimulated nerve segment and prolonged neuromuscular blockage may also contribute to false positives. Therefore, we should try to remove the surrounding tissues and blood clots adjacent to the RLN before detection and stimulate the nerve itself rather than the surrounding tissues, increase the stimulation current if necessary, or replace the stimulation electrodes and connecting wires. Furthermore, the use of muscle relaxants and sevoflurane should be avoided during thoracic phase surgery. False-negative cases (VCP with good EMG) can occur with RLN injury after the last detection due to progressive edema or nonsurgical problems, such as accidental injury during neck surgery or dislocation of the arytenoid cartilage. In this study, we did not strictly adhere to the algorithm proposed by guidelines but improved IONM detection steps, and we found the incidence of NPV and PPV acceptable, indicating that IONM is feasible in minimally invasive McKeown esophagectomy.

This study has several limitations. First, it is a retrospective study, and although the baseline characteristics between the two groups were similar, selective sample bias may exist. The IONM group has only been applied since 2018, thus, learning curve effect with more experience in surgical technique may contribute to a better outcome in the IONM group. Large-scale randomized controlled studies are still needed. In addition, we did not use IONM to detect the RLN after thoracic phase surgery. The RLN in false-negative cases may be injured during cervical anastomosis. Although we found a significant difference in dissected RLN lymph nodes, survival analysis was not performed to evaluate the advantages of IONM.

CONCLUSION

We illustrated the feasibility and efficacy of IONM in this study. IONM showed advantages for distinguishing RLN, achieving thorough mediastinal lymphadenectomy with less RLN injury and providing an accurate prediction of postoperative VCP incidence in minimally invasive McKeown esophagectomy.

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