Original Article

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Comparison of Outcomes of Intra-operative Neuromonitoring of Recurrent Laryngeal Nerve Versus Visualisation Alone during Thyroidectomies: A Singapore Experience

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Abstract

Introduction: Although intra-operative neuromonitoring (IONM) has become commonly used to identify the recurrent laryngeal nerve (RLN) during thyroid surgeries, its value is still debatable. This study aimed to evaluate the outcomes of thyroid surgery using IONM versus visualisation alone (VA).

Methods: We conducted a retrospective analysis of all the open thyroidectomies performed by the otolaryngology department in a tertiary institution in Singapore (Khoo Teck Puat Hospital) from 1 January 2014 to 31 December 2018. There were 301 nerves-at-risk (NAR), 139 in the IONM group and 162 in the VA group. The primary outcome measure was the incidence of RLN injury and the secondary outcome measure was operative duration.

Results: There were 33 NAR with immediate post-operative RLN injury, of which 7 had permanent (>6 months) injury. There were minor improvements in the respective rates of immediate and permanent injury in the IONM group (7.9%, 0.7%) compared to the VA group (13.6%, 3.8%), but these were not statistically significant (*P*=0.14, 0.13). The average operative duration of total thyroidectomies in the IONM group was 37 minutes shorter than in the VA group, but the difference was not statistically significant (*P*=0.40).

Conclusion: The current study shows that the use of intra-operative neuromonitoring shows a tendency towards better RLN outcome and operative duration for total thyroidectomies, but the study may be too small to demonstrate a statistical difference.

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Keywords: Nerve monitoring, otorhinolaryngology, surgery, thyroid, vocal cord paralysis

Introduction

Thyroid surgery is one of the most common head and neck procedures performed in any otolaryngology department.[1] Although the incidence is low, it is well known that injury to the recurrent laryngeal nerve (RLN) is one of the most serious complications from thyroid surgery, as it results in significant morbidities for the patient (e.g. hoarseness, dysphagia, aspiration). It is therefore unsurprising that iatrogenic vocal cord (VC) palsy is the leading cause of medico-legal claims following thyroid surgery.[2]

The reported rates of RLN injury in the literature vary. Some studies quote an overall risk of 2.3–26%,[3] with 2–8%[4-6] being transient and 0.5–3%[4-6] being permanent. The gold standard of RLN preservation during thyroid surgery is routine visual identification of the nerve. Lee and Siow reported that the incidence of transient and permanent RLN injury was 8.2% and 0.9%, respectively, using visualisation alone (VA). However, visualisation may not be straightforward in difficult cases or if the surgeon is in a low-volume centre. In recent years, intra-operative neuromonitoring (IONM) has become increasingly more popular to assist the surgeon with reliably identifying the nerve[8] and alerting him/her of impending neuropraxia from accidental injury. More than just a tool for identification, it assists in verifying and documenting nerve function and integrity objectively (useful medico-legally), as it has a high predictive value with regard to the expected VC function.[9-11] However, the use of neuromonitoring is

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associated with disadvantages such as a longer set-up time[12] and increased cost of surgery.[13] Furthermore, the current literature on neuromonitoring is inconclusive on its ability to prevent RLN injury and shorten operative time, with some studies showing a modest difference and others concluding no difference.[14] In the face of conflicting evidence, some thyroid surgeons may choose not to use neuromonitoring despite its potential benefits. The question whether IONM use in thyroidectomies leads to better outcomes therefore continues to be of interest to many researchers. Although considerable data from other countries has been published, the outcomes in Southeast Asia have not been previously described. Given the increasing usage of neuromonitoring for thyroid surgery both in Asia and across the globe, the authors conducted the current study to investigate the outcomes of thyroidectomies in a tertiary institution in Singapore (Khoo Teck Puat Hospital) with the use of IONM and without (i.e. VA).

We chose 2 outcome measures that we felt were important and quantifiable: the primary aim was to compare the incidence of RLN injury and the secondary aim was to compare the operative duration between the 2 groups.

Methods

We conducted a retrospective cohort study of all open thyroidectomies performed by the otolaryngology department of a single institution between 1 January 2014 and 31 December 2018. Being a public institution dedicated to nurturing otolaryngology residents, this was by and large a trainee-supervised practice. The surgeries were performed by various surgeons within the department (senior residents under consultant supervision or consultants themselves) and we did not take into account the seniority of the surgeon as it was not an aim of the study. The selection criteria for whether IONM was used was based on the surgeon's preference.

Patients who had undergone isthmusectomies and parathyroidectomies alone were not included in the analysis. We excluded patients with an intentionally sacrificed RLN (n=1), a pre-existing RLN palsy (n=2), and those without a post-operative immediate laryngoscopic evaluation (n=10)

All included patients had a routine pre-operative laryngoscopic examination to evaluate VC mobility, which was repeated within 24 hours after the surgery on post-operative day one (POD1) to check RLN function. Patients were deemed to have immediate palsy if they exhibited any form of VC weakness (paresis) or complete immobility (paralysis) for the purposes of this study. VC paresis was defined as a hypomobile VC that included sluggish motion of the affected VC on repetitive phonation or a perceived asymmetry between VC on abduction and adduction. This was regardless of subjective vocal outcome. Patients with immediate palsy were followed up in the outpatient clinic to determine if their palsy recovered. If the palsy recovered within 6 months, the patient was deemed to have a transient palsy and if the palsy was still present at 6 months, they were deemed to have a permanent palsy.

For each patient, we recorded whether the nerve monitor was used, the operative duration, as well as parameters such as age, gender, size of the nodule/gland, histological diagnosis and any history of previous thyroid surgeries. Unfortunately, loss of signal (LOS) was not routinely recorded in all cases, and it was not possible to correlate post-operative nerve function with intra-operative LOS. The IONM model used in our study was the Nerve Integrity Monitor (NIM)-Response 3.0® (Medtronic, Jacksonville, US), which is a form of intermittent neuromonitoring. If neuromonitoring was used, the patient was intubated with a NIM Trivantage® (Medtronic, Minneapolis, US) electromyography endotracheal tube to facilitate usage of the IONM. The tube was placed with the middle of the blue-marked region (3cm of the exposed electrodes), well in contact with the true vocal cords under direct laryngoscopy. The impedance of the electrodes was checked prior to commencement of surgery. No muscle paralytic agents were used when IONM was set up. Regardless of whether neuromonitoring was used, the RLN were routinely identified by visualisation.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 17 (IBM Corp, Armonk, US). A value of $P<0.05$ was considered statistically significant. The study was approved by the national ethics board (National Healthcare Group Domain Specific Review Board). The need for individual patient consent was waived as the study was done on non-identifiable data.

Results

There were 261 thyroidectomies included in the study, with 108 performed under neuromonitoring and 153 using VA. There were 221 hemi and 40 total thyroidectomies, giving a count of 301 NAR. A hemithyroidectomy was counted as 1 NAR and a total as 2 NAR. The mean age in the study was 49 years old; 74% (n=193) of all thyroidectomies were performed on female patients. The histological diagnosis was malignant in 66 (25.3%) of the cases (inclusive of incidental micropapillary thyroid cancers). Table 1 summarises the demographics of the patients in each group. Both the IONM and VA

Table 1. Demographics of patients

	Overall (n=261)		IONM (n=108, 41.4%)		VA (n=153, 58.6%)	
	No. of Patients (n)	Proportion (%)	No. of Patients (n)	Proportion (%)	No. of Patients (n)	Proportion (%)
Gender – female	193	73.9	89	82.4	104	68.0
Mean age, years ± SD	49.2±12.5		48.2±13.4		49.9±11.8	
Histology – malignant	66	25.3	33	30.6	33	22.6
Nodule size ≥4cm*	126	48.3	52	48.1	79	51.6
Revision surgery	21	8.0	9	8.3	12	7.8
With central (with or without) lateral neck dissection	11	4.2	9	8.3	2	1.3

IONM: intra-operative neuromonitoring; N: number of patients; SD: standard deviation; VA: visualisation alone
*Diffusely enlarged lobes were considered as nodule size ≥4cm to facilitate statistical analysis.

groups had fairly similar characteristics in terms of age, gender, histological diagnosis, nodule size and history of previous surgery.

Analysis of post-operative RLN palsy

In the IONM group, there were 11 immediate RLN palsies (7.9%), of which 1 (0.7%) was permanent. The rate of RLN palsy was slightly higher in the VA group, with 22 immediate palsies (13.6%), of which 6 were permanent (3.8%) (Fig. 1). Three patients in the IONM group and 2 patients in the VA group were lost to follow-up before the 6 months period; thus it was not possible to determine if their immediate palsy showed any recovery. The difference in palsy rates between the 2 groups was not statistically significant.

The risks of immediate and permanent palsies in the IONM group were not found to be significantly lower than in the VA group (immediate odds ratio (OR) 0.58 [95% confidence interval (CI), 0.29–1.16]; permanent OR 0.20 [95% CI, 0.02–1.61]) (Tables 2 and 3). Multivariate logistic regression analysis was only performed for immediate palsies as the sample size for permanent palsies was too small to perform a reliable multivariate analysis. Adjustments for potential confounders, such as age, gender, malignant

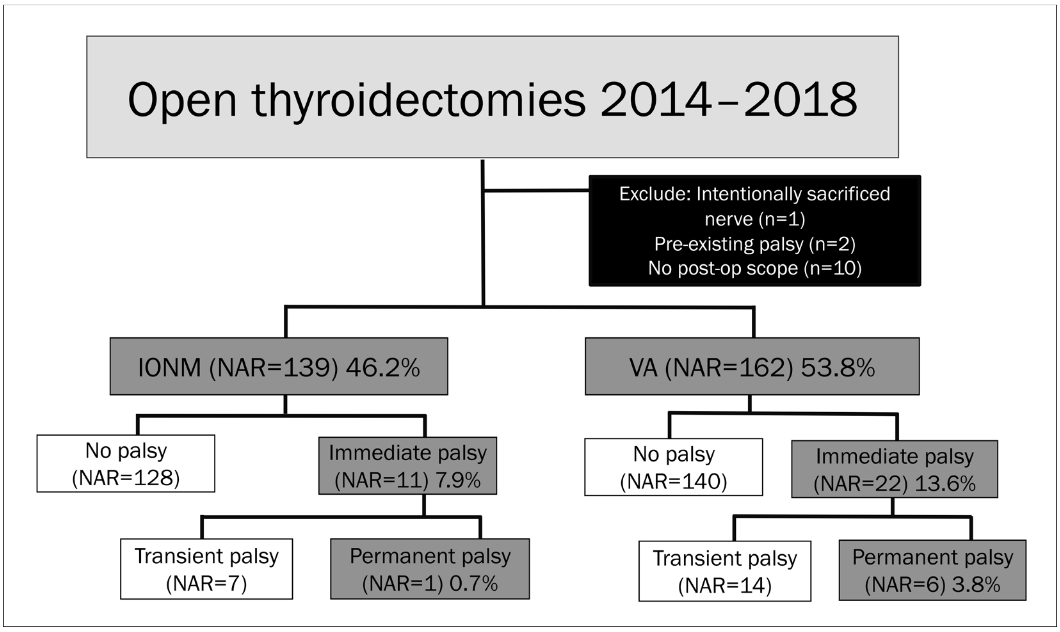

Fig. 1. Results of RLN palsy
*3 and 2 immediate palsy NARs were lost to follow-up in the IONM and VA groups, respectively.
IONM: intra-operative neuromonitoring; NAR: nerves-at-risk; VA: visualisation alone

histology, large nodules and neck dissection status, did not show any difference between the 2 groups to be statistically significant (OR 0.54 [95% CI, 0.24–1.22]) (Table 2).

Analysis of operative duration

For the analysis, we excluded 14 cases where other concurrent procedures (e.g. neck dissection) were done. After exclusion, we had a total of 216 hemi and 31 total thyroidectomies (Table 4). The operative duration was defined as the time taken from skin incision to closure.

The mean duration for hemithyroidectomies was approximately equivalent in both groups but shorter in the IONM group by 37 minutes for total thyroidectomies (Fig. 2). Statistical tests for the total thyroidectomy subgroup did not show any statistically significant difference in the operative duration with or without IONM. The Mann-Whitney-U test gave a P value of 0.40, which was not significant ($P>0.05$). A multivariate logistic regression analysis adjusting for potential confounders (those previously mentioned in the analysis of post-operative RLN palsy) gave a non-significant P value of 0.68 (95% CI, 0.33–2.07).

Discussion

Our study found that IONM reduced the rates of RLN palsy, but like many of the other studies, the results did not reach statistical significance.[15-18] This is most likely because RLN palsy is a rare complication and only a study with a very large sample size may show statistical significance. Post-hoc sample size calculation showed that we would need a sample size of NAR=942 (434 IONM, 508 VA) to detect a statistical difference given the rates of RLN palsy in our study. However, even in one of the largest single-institution retrospective studies with a total number of 2,034 patients, the authors found no significant difference in the RLN palsy rates with or without neuromonitoring.[13] Pooled data from multiple centres may help to resolve issues of low statistical power in single-institution studies. While some large multicentre trials have shown a decrease in the palsy rates with neuromonitoring, they are contradicted by others.

Meta-analyses can help to increase the sample size greatly, but interpretation of the results may be limited by the heterogeneity and quality of the studies included. A recent Cochrane meta-analysis of 5 randomised controlled trials (RCTs) did not show any significant difference in the rates of RLN palsy with or without neuromonitoring,[13] but concluded that the study was limited by the small sample size and overall low number of events in the included trials. However, another meta-analysis by Bai et al. managed to show significant reduction in both immediate and permanent palsy rates with IONM, using a very large pooled sample of 59,380 patients from a mixture of 34 RCTs, case controls and cohort studies.[19]

Some studies have shown that IONM help to mitigate the increased risk of RLN palsy in high-risk surgeries,[20] but a subgroup analysis of 113 high-risk NAR (defined as re-operations, malignant histology or thyroiditis) in our study population did not show any difference, likely due to the small sample size.

The immediate post-operative RLN palsy rate in our study falls within the higher end of the range traditionally quoted in literature. This was probably attributable to 2 main reasons. Firstly, our definition of 'palsy' was broadly defined as any subjective endoscopic ipsilateral weakness in VC movement including VC paresis and paralysis (not every study stated their definition of 'palsy'). Our broad inclusion criterion was deliberately set in order to maximise the number of palsy cases for statistical analysis, given the relatively small total number of NAR. Secondly, we routinely examined all cases post-operatively with a flexible laryngoscope, which would have picked up any asymptomatic RLN palsy (where the contralateral cord was compensating well), resulting in a more accurate diagnosis. Studies have shown that the sensitivity of voice change in predicting VC paralysis ranged from just 33% to 68%,[21,22] which suggest why recent series that comprehensively examined post-operative RLN injury quoted higher rates of nearly 10%.[3,6]

The analysis for operative duration showed that there was negligible difference with or without neuromonitoring for hemithyroidectomies, although in theory IONM should be expected to decrease the operative duration. We obtained this result probably because 90% of our hemithyroidectomies were primary, uncomplicated surgeries. Therefore, RLN identification would likely have been easier and hence the time difference with or without neuromonitoring may be minimal. However, we postulate that if more of our hemithyroidectomies were completion or high-risk cases, the amount of time saved might have been greater. For total thyroidectomies, because of the need to identify 2 nerves, the time saved using a nerve monitor was greater. However, the significance of this result was probably reduced by the relatively small number of total thyroidectomies in our study (n=31).

A limitation of our study, other than the low statistical power, was the lack of randomisation, which could have introduced a selection bias. This was unavoidable given the study's retrospective design, but the characteristics of patients in each group were found to be comparable (Table 1), which would hopefully limit the bias in this study.

Table 2. Analysis of immediate RLN palsy

Variable		Incidence of Immediate Palsy Per NAR	Univariate Analysis		Multivariate Analysis*	
			OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Use of nerve monitor	IONM	11/139 (7.9%)	0.58 (0.29–1.16)	0.12	0.54 (0.24–1.22)	0.14
	VA	22/162 (13.6%)	1		1	

CI: confidence interval; IONM: intra-operative neuromonitoring; NAR: nerves-at-risk; OR: odds ratio; VA: visualisation alone
*Multivariate analysis performed using age, gender, histology, nodule size and neck dissection status as the other variables.

Table 3. Analysis of permanent RLN palsy

Variable		Incidence of Permanent Palsy Per NAR	Univariate Analysis	
			OR (95% CI)	*P* Value
Use of nerve monitor	IONM	1/136 (0.7%)*	0.20 (0.02–1.61)	0.13
	VA	6/160 (3.8%)*	1	

CI: confidence interval; IONM: intra-operative neuromonitoring; NAR: nerves-at-risk; OR: odds ratio; VA: visualisation alone
*5 patients with immediate palsy were lost to follow-up (2 VA, 3 IONM) and excluded from analysis.

Table 4. Analysis of operative duration

Type of Thyroidectomy	Mean Duration (Min)		Mann-Whitney U Test	Multivariate Analysis
Total n=31	IONM = 279 VA = 316	37min shorter with IONM	*P*=0.40	RR 0.32 (*P*=0.68; 95% CI 0.33–2.07)
Hemi n=216	IONM = 110 VA = 108	2min longer with IONM	*P*=0.74	RR 1.04 (*P*=0.81; 95% CI: 0.78–1.38)

CI: confidence interval; IONM: intra-operative neuromonitoring; RR: relative ratio; VA: visualisation alone

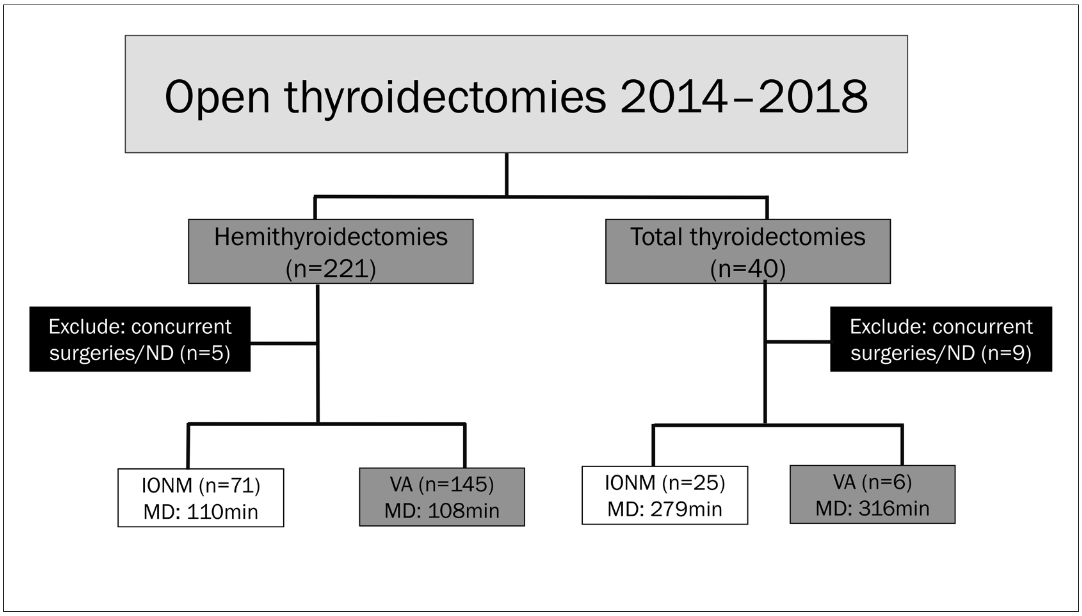

Fig. 2. Results for operative duration
ND: neck dissections; MD: mean duration; IONM: intra-operative neuromonitoring; VA: visualisation alone

Despite the inability to prove a statistically significant difference with IONM in this study, it must be recognised that there are certain intangible and difficult-to-quantify benefits of IONM that were not studied. Firstly, the level of stress reduction when the surgeon is struggling with a challenging or long case cannot be underestimated. Secondly, in our experience, IONM has helped to correctly identify the RLN in cases of anatomical nerve variation (such as multiple RLN branching, distorted nerve anatomy from previous surgery, non-recurrent laryngeal nerve), which could have easily resulted in visual misidentification. Lastly, there is an unmistakable benefit of being able to objectively document a nerve signal at the end of surgery, in the event that medico-legal challenges arise.

Conclusion

In conclusion, there was no statistical difference in the recurrent laryngeal nerve injury rate or the operative duration with or without nerve monitoring in this study. However, the study may have been underpowered given its relatively small sample size. Although outcomes of IONM have been extensively published internationally, this is the only Southeast Asian study on this topic to the best of our knowledge, where all subjects had a flexible laryngoscopy done immediately post-operatively for visual correlation. This valuable data from a previously unstudied region will help us better understand IONM outcomes across the globe. Further large-scale, randomised controlled trials may be conducted with closely matched groups to evaluate the benefits of IONM.

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