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Review

# Systematic review and meta-analysis on intra-operative neuro-monitoring in high-risk thyroidectomy

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## HIGHLIGHTS

- First meta-analysis on use of neuro-monitoring during high-risk thyroidectomy.
- Intra-operative neuro-monitoring decreased vocal cord palsy in high-risk thyroidectomy.
- Neuro-monitoring should be used in re-operation and thyroidectomy for malignancy.

## ARTICLE INFO

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## ABSTRACT

*Introduction:* Use of intra-operative neuro-monitoring (IONM) during high-risk thyroidectomy has been suggested to decrease the rate of recurrent laryngeal nerve (RLN) palsy. However, current evidences were mixed and there was no large-scale study concluding its benefit. We evaluated the role of IONM in reducing RLN palsy during high-risk thyroidectomy and identified which high-risk subgroup would be most benefited.

*Methods:* A systemic review was performed to identify studies comparing the use of IONM and visual identification of RLN alone (VA) during high-risk thyroidectomy, namely re-operation, thyroidectomy for malignancy, thyrotoxicosis or retrosternal goitre. Rate of RLN palsy was presented in terms of number of nerve-at-risk (NAR). Meta-analysis on overall high-risk thyroidectomy and subgroups were performed using fixed or random-effects model.

*Results:* Ten articles were eligible for final analysis. There were 4460 NARs in VA group and 6155 NARs in IONM group. Comparing to VA, IONM had lower rate of overall [4.5% vs. 2.5%, Odd ratio (OR): 1.40, 95% confidence interval (CI): 1.12–1.79, $p = 0.003$] and temporary [3.9% vs. 2.4%; OR: 1.47, 95% CI: 1.07–2.00, $p = 0.016$] RLN palsy in overall high-risk thyroidectomies. On subgroup analysis, although numbers of NARs were less than minimal numbers required for a statistical powered study (2.1%–72.7%), use of IONM decreased the rate of overall RLN palsy during re-operation (7.6% vs. 4.5%, OR: 1.32, $p = 0.021$) and temporary RLN palsy during thyroidectomy for malignancy (3.1% vs. 1.6%, OR: 1.90, $p = 0.026$). Use of IONM tended to have a lower rate of overall RLN palsy during thyroidectomy for malignancy than VA alone. (3.5% vs. 2.1%, $p = 0.050$).

*Conclusions:* Selective use of IONM during high-risk thyroidectomy decreased the rate of overall RLN palsy. IONM should be applied during re-operative thyroidectomy and thyroidectomy for malignancy.



## 1. Introduction

Recurrent laryngeal nerve (RLN) palsy is one of the major morbidities after thyroidectomy. It results in hoarseness of voice, choking and aspiration in unilateral palsy. If both RLNs were paralysed, patients would suffer from potential fatal airway obstruction. RLN palsy not only affects quality of life, but also incurs more charges for health care [1,2]. For thyroid surgeons, it is the major cause of litigation after thyroidectomy [3]. Technique of intra-operative neuro-monitoring (IONM) of RLN during thyroidectomy was first described in 1970s. IONM aids localisation of RLNs during thyroidectomy and facilitates identification of

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anatomical variation of RLN. It is believed that use of IONM can decrease the rate of RLN palsy. While post thyroidectomy RLN palsy is uncommon, ranged from 1.25% to 3.9% [4–6], previous studies have showed that routine application of IONM in all thyroidectomy did not decrease the rate of RLN palsy and it is not cost effective. Three meta-analysis with more than 3000 nerve-at-risks have failed to demonstrate any benefits in routine use of IONM during all thyroid surgeries [7–9].

On the other hand, use of IONM during high-risk thyroidectomy have been advocated. Re-operation, thyroidectomy for malignancy, thyrotoxicosis and retrosternal goitre were considered as high-risk thyroidectomy which the rate of RLN palsy were higher [10–14]. In re-operation thyroidectomy, presence of scar and anatomical distortion made routine dissection and identification of RLN difficult. The risk of RLN injuries were higher if surgeons fail to identify RLNs [10]. There were 4.6–10.4 times risk in having post-operative RLN palsy compared with primary operation [10,13]. For thyroidectomy for malignancy, locally advance pathology and associated lymph node dissection added the risk to RLN palsy [15]. Comparing to thyroidectomy for benign goitre, operation for malignancy had a relative risk of 2.0–5.4 in developing RLN palsy [10,13]. In view of high incidence of RLN palsy and needs of RLN localisation, selective use of IONM during high-risk thyroidectomy is suggested [16]. Some studies have showed that use of IONM during thyroidectomy for recurrent goitre or malignancy decreased the rate of RLN palsy [17–20]. However, other studies reported that there was no significant improvement if IONM was applied [10,21–24]. Due to relatively small sample size, power and their conclusion have been questioned. In this study, we aimed to evaluate the role of IONM in decreasing RLN palsy during high-risk thyroidectomy. We performed a subgroup analysis and evaluated which high-risk subgroup would be most benefited in using IONM.

## 2. Methods

This systemic review and meta-analysis were conducted in accordance with the PRISMA statement [25].

### 2.1. Search strategy

Studies comparing RLN palsies between use of IONM and visualization of RLN alone (VA) during thyroidectomy were retrieved from Pubmed, Medline, Embase and Cochrane central register of clinical trials (CENTRAL) on 18th September 2015. We used the following free text search terms in “All fields”.

#1 “Thyroid Surgery “ OR “ Thyroidectomy”
#2 “Intra-operative neuro-monitoring” OR “Recurrent laryngeal nerve monitoring”
#3 “High risk” OR “Re-operation” OR “cancer” OR “carcinoma” OR “thyrotoxicosis” OR “Toxic goitre” OR “retrosternal” OR “substernal”

We used a combination of #1, #2 and #3 in literature search. There was no language restriction or methodological filters. Studies published dated from 1st January 2000 to 30th June 2015 were included. The bibliographies of five previous meta-analysis were reviewed and looked for relevant references. [7,9,26–28].

### 2.2. Study selection

All titles identified were screened independently by two authors (K.P.W. & K.L.M.). Results were compared and any disagreements were resolved by consensus. Abstract of any potential articles were reviewed, eligible studies were selected for full article review.

Studies were included in the meta-analysis if they met the following criteria.

1 Full English-language article on human patients.
2 Any randomized control trial, prospective or retrospective comparative studies comparing the rate of RLN palsy between thyroidectomy with VA and IONM.
3 Thyroidectomy in patients with history of thyroid surgery, thyroidectomy for thyroid cancer, thyrotoxicosis or retrosternal goitre
4 Data on number of RLN at risk and RLN palsy that could be extracted from published manuscript for calculation.
5 Number of post-operative RLN palsy was determined by laryngoscopy.

Case reports, editorials, expert opinions and reviews without original data were excluded. In case of potential duplicate data from same authors and center, studies with most representable data were selected for analysis. Newcastle-Ottawa Scale (NOS) assessed quality of study.

### 2.3. Data extraction

All data were extracted onto a standardized form. Primary data included type or design of study, first authorship, country of origin, year of publication, patient demographics, history of previous thyroidectomy, presence of thyroid cancer, thyrotoxicosis, retrosternal goitre, neuro-monitoring machine, electrode applied, stimulation current applied, site of nerve stimulation, extent of thyroidectomy, number of patients, number of RLN at risk, definition and number of temporary and permanent RLN palsy. Rate of RLN palsy was calculated with the total number of nerves-at-risk (NARs) as the denominator. Temporary and permanent RLN palsy was defined according to definition of the original article, and overall RLN palsy was the sum of temporary and permanent palsy. Data were also stratified into four subgroups, namely re-operation (thyroidectomy was preformed in patients with history of previous neck operation), malignancy (thyroidectomy was preformed for malignant thyroid cancer), thyrotoxicosis and retrosternal goitre for sub-group analysis.

### 2.4. Statistical analysis

All individual outcomes were integrated with the meta-analysis software Review Manager Software 5.0 (Cochrane Collaborative, Oxford, England). Odd ratios (OR) were calculated for rate of RLN palsy. Heterogeneity was assessed with $I^2$ test by both fixed and random-effects model [29]. Any $I^2$ test > 50% was considered substantial heterogeneity. Fixed-effect models were used for analysis. If $I^2$ test for fixed-effect models >50%, random-effects model were applied. Publication bias was assessed using Begg's rank correlation test and Egger's regression test. Analysis was performed in overall patients and aforementioned four subgroups. The statistical analysis was performed using the IBM SPSS version 20.0 (IBM, Armonk, NY) and Comprehensive Meta-Analysis Version 2.2.064 (Biostat, Inc., Englewood, NJ). P-value < 0.05 was considered as statically significant.

## 3. Results

Fig. 1 shows the PRISMA flowchart of article selection. After initial search, 249 articles were identified and 10 articles were retrieved from five other meta-analysis [7,9,26–28]. 75 articles were found to be duplicated and thus excluded. After screening title, 42 non-English and 92 irrelevant articles were excluded. On