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

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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.

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 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.

METHODS:

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

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]

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.

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.

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.

RESULTS

Figure 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 screening abstract of 50 articles, 28 articles were excluded, as they did not fulfil the selection criteria. 22 articles remained and were assessed in full-text. Among them, 12 articles were further excluded, in which 4 articles had data presented later in a more representative article [12, 30-32], 3 articles were not assessing RLN palsy in high-risk thyroidectomy [33-35], no data can be extracted in 3 articles [11, 36, 37] and no full manuscript was available in 1 article [38]. One study which laryngoscopy was not routinely performed was also excluded [19]. Therefore, ten studies were included for final analysis.

Study Characteristics

Table 1 shows the study design, distribution of high-risk subgroups, quality of study and number of nerve-at-risk in ten included studies. Two prospective comparative studies and eight retrospective studies were included. The comparison of thyroidectomy with VA against IONM in "re-operation", "malignancy", "thyrotoxicosis" and "retrosternal goitre" subgroups were reported in 7, 6, 4, 2 articles respectively. Data were extracted for pooling and analysis. However, Atallah et al did not report the rate of RLN palsy of each subgroup [22]. Therefore, its data was not included for subgroup analysis. According to data pooling from 10 studies, there were 4460 NARs in VA group, and 6155 NARs in IONM group.

Comparing between VA and IONM group, there were no difference on baseline demographic and clinic-pathological data in six articles. Comparing to VA group, three studies have shown that duration of operation with IONM was longer [21, 23, 39]. In contrast, despite more bilateral thyroidectomy were performed in IONM group, Barczynski et al reported that use of IONM had a shorter duration of operation in a study on re-operative thyroidectomy[20]. (94.5+/- 23.0 mins. vs. 88.3 +/- 23.3 mins, $p<0.001$)

Table 2 shows timing of initial post-operative laryngoscopic assessment, definition of permanent recurrent laryngeal nerve palsy, set-up and application of intra-operative neuro-monitoring (IONM). Routine pre-operative laryngoscopies were performed in all studies. For post-operative laryngoscopy, all studies performed post-operative laryngoscopic examination to evaluate vocal cord function from immediate after operation to within 2 weeks after operation. Permanent RLN palsy was defined as RLN palsy that did not recover within 12 months in 6 studies and 6 months in 2 studies. On the other hand, temporary RLN palsy was defined as recovery of RLN function within 12 months in 6 months and 6 months in 2 studies. In the study by Prokopakis et al, all patients with RLN palsy recovered by 4 months [39].

For IONM, insertion of needle electrodes into vocal cord was reported in 5 studies, which all of them were at the early phase of studies [10, 18, 20, 22, 23]. Surface electrode integrated into endotracheal (ET) tube was used in 7 studies. Electrodes were connected to Neurosign 100 system (Magstim Clarify Company, Whitland, UK) in 5 studies, and NIMS response 2.0 or 3.0 Nerve monitoring systems (Medtronic, Jacksonville, FL, US) in 7 studies. Stimulation current ranged from 0.05 to 5 mA. Pre-dissection vagal stimulations as suggested by guideline from International Neural Monitoring Study Group (INMSG) were performed in 4 studies [40]. Both direct (RLN) and indirect (vagus) nerve stimulation were applied in 7 studies.

Analysis on heterogeneity

Heterogeneity was observed in temporary RLN palsy in "re-operation" subgroup (I^2: 63.0%) and overall RLN palsy in "thyrotoxicosis" subgroup (I^2: 51.3%). Therefore, we adopted random-effect models in these subgroup analyses.

Overall high-risk thyroidectomy

Results from 10 studies were pooled up. There were 4460 NARs in VA group, and 6155 NARs in IONM group. Rate of overall [4.5%, (201/4460) vs. 2.5% (151/6155), Odd ratio (OR): 1.42, 95% confidence interval (CI): 1.12 – 1.79, p=0.003] and temporary [3.9% (129/3332) vs. 2.4% (71/3017); OR: 1.47, 95% CI: 1.07 – 2.00, p=0.016] RLN palsy were higher in VA group than IONM group. (Figure 2) Permanent RLN palsy was comparable between two groups. [1.6% vs. 1.3%, OR: 1.33, 95% CI: 0.94 - 1.88, p=0.104] No publication bias was found by Begg analysis and Egger regression test on meta-analysis. (P > 0.05)

Re-operation

In seven included studies, three of them clearly stated that RLNs were at risk in a previously operated field [20, 23, 39], while others did not describe whether the NAR was at the previously explored side or the contra-lateral side [10, 16, 21, 41]. Barczynski et al reported that IONM had a lower rate of overall (4.0% vs. 8.7%, p=0.001) and temporary (6.3% vs. 2.6%, p=0.003) RLN palsy than VA.[14] On meta-analysis, the rate of overall RLN palsy [7.6% (114/1497) vs. 4.5% (78/1751), OR: 1.48, 95% CI: 1.06 - 2.06, p=0.021] is lower in IONM group than VA group. (Figure 3) Permanent (2.7% vs. 2.5%; OR: 1.40, 95% CI: 0.98 to 2.47, p=0.171) and temporary RLN palsy (6.3% vs. 4.3%, OR: 1.24, 95% CI: 0.52 to 2.97, p= 0.631) were comparable. No publication bias was found. (P > 0.05)

Malignancy

Data from five articles were pooled for analysis. The rate of temporary RLN palsy was significantly higher in VA group than in IONM group [3.1% (36/1160) vs. 1.6% (21/1282), OR: 1.90, 95% CI: 1.08 to 3.35, p=0.026]. However, the rate of overall RLN palsy (3.5% vs. 2.1%, OR: 1.52, 95% CI: 0.98 to 2.36, p=0.050) and permanent RLN palsy (3.1% vs. 1.6%, OR: 1.1, 95% CI: 0.61 to 2.11, p=0.696) were comparable. (Figure 4) Publication bias was noted at analysis on permanent RLN palsy by Egger Regression test (t-value = 3.956, p= 0.029).

Thyrotoxicosis

Pooled data of three articles showed 1166 NARs in VA group and 1836 NARs in IONM group [12, 16, 41]. The rate of overall RLN palsy (1.1% vs. 0.7%, OR: 1.33, 95% CI: 0.41 to 4.36, p=0.640), permanent (0.6% vs. 0.2%, OR: 3.57, 95% CI: 1.00 to 12.76, p=0.051) and temporary RLN palsy (0.8% vs. 1.2%, OR: 0.60, 95% CI: 0.21 to 1.71, p= 0.338) were not significantly different. No publication bias was found. ($P > 0.05$)

Retrosternal goitre

Only one study by Chan et al reported the rate of RLN palsy in thyroidectomy for retrosternal goitre [16]. Rate of overall (7.7% vs. 3.4%, p=0.317), temporary (7.7% vs. 1.7%, p=0.128) and permanent RLN palsy (0% vs. 1.7%, p=0.346) were comparable between VA group and IONM group.

DISCUSSION

Two previous meta-analysis reviewing the role of rountine IONM in all thyroidectomy have performed subgroup analysis on high-risk thyroidectomy. Higgins et al defined re-operation and thyroidectomy for malignancies, thyrotoxicosis or retrosternal goitre as high-risk thyroidectomy. They found that there were no benefits in using IONM in high-risk thyroidectomies [7]. However, it has been criticized for inclusion of non-comparative studies and case reports in the study. Pisanu et al reported another meta-analysis and showed similar findings [9]. With IONM, overall, temporary and permanent RLN palsy were comparable to thyroidectomy without IONM. To report a statistically representative study evaluating the role of IONM, around 9000 NARs were required [11]. However, the sample size in meta-analysis by Pisanu et al (around 3300 NARs) was much lower than suggested. Therefore, non-beneficence in using IONM during high-risk thyroidectomy cannot be concluded. To our knowledge, our study is the first meta-analysis focusing on the use of IONM in high-risk thyroidectomy. We also evaluated which subgroup of high-risk thyroidectomy would be benefited. We have applied stringent selection criteria and included up-to-date publications. Total number of nerve-at-risk included was about 10500. We believed that this meta-analysis is a statistically powered study to evaluate whether IOMN should be used during high-risk thyroidectomies.

From our results, applications of IONM can lower the overall and temporary RLN palsy during high-risk thyroidectomy. Although the number of NARs in this meta-analysis was less than the minimal number of NARs required, we still demonstrated statistically significant improvement of overall and temporary RLN palsy with the use of IONM. (Table 3) Therefore, we recommended routine use of IONM during high-risk thyroidectomies.

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There was a strong debate on whether IONM is beneficial during re-operation in recent literatures [19, 20, 23, 39]. In subgroup analysis, we cannot demonstrate any benefits in either permanent or temporary RLN palsy. For a sufficiently powered comparison, 4744 and 7561 NARs were required for permanent and temporary RLN palsy respectively. (Table 3) However, there were only 10.7-35.6% of the required NARs available for meta-analysis. As this subgroup analysis is considered underpowered due to small sample size, we cannot deny or support the positive role of IONM in terms of temporary or permanent RLN palsy. However, we confirmed that applications of IONM decreased overall RLN palsy. (OR: 1.32, p = 0.021). It could be due to relative higher sample size to achieve a statistically significant result. (35.7% - 41.7%) On the other hand, half of the studies did not state whether re-operation was performed on the previously explored side [10, 16, 21, 41]. These results might overlook the benefit of IONM. Therefore, the result should be interpreted cautiously. Future prospective controlled studies focusing on re-operation in a previously operated field would be worthwhile in evaluating the benefit of IONM.

For thyroidectomy on malignancy, although the rate of permanent RLN palsy did not decrease if IONM was used, there was publication bias observed in this analysis. Despite insignificance of odds ratio (p-value = 0.696), we should be cautious with the pooled estimates of permanent RLN palsy in this subgroup analysis. In view of benefits on temporary and potential overall RLN palsy, routine use of IONM during thyroidectomy for malignancy should also be supported. For toxic goitre, rate of RLN palsy was 0.8% in pooled data of 3 included studies. To demonstrate its benefit on overall RLN palsy, 26000 NARs for each group were needed. (Table 3) A study to evaluate the benefits of IONM in this group might not be practical and worthwhile.

We realized that there were some drawbacks in our analysis. As majority of the studies were retrospective & observational, they were prone to be difficult in interpretation with bias. Therefore, the findings were weaker than a meta-analysis including prospective randomized controlled trials (RCT). However, to our knowledge, there were no prospective RCTs focusing on high-risk thyroidectomy available in the literature. Secondly, there were large heterogeneities between studies. This was related to diversity in patients recruited, operative techniques and the way IONM applied. Bias in patients' allocation was also present. It reflected by the fact that more extensive surgery (in term of bilateral surgery and total thyroidectomy) was performed in IONM group [20, 21, 23], and IONM was more likely to be used in later part of the study [17, 18, 20, 21]. Although guideline on IONM by INMSG that aimed to standardize the technique was published in 2011, most patients in this study were recruited before that. Algorithm of IONM including pre-dissection vagal stimulation and site of nerve stimulation varied in different centers. All these factors led to a large heterogeneity in the analysis. By analyzing the results with random-effect model, we minimized the effect of heterogeneity on our results.

In this meta-analysis, all included studies evaluated the use of intermittent IONM. There was a risk of RLN injury before identification or in-between nerve stimulations [42]. Nowadays, continuous neuro-monitoring of RLN have gained increasing interests as it provides a real-time feedback to surgeons to avoid RLN injuries. Further studies are needed to evaluate whether continuous neuro-monitoring provides superior protective effect to intermittent IONM or visual identification of RLN alone in the high-risk thyroidectomy.

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CONCLUSON

Routine identification of RLN remains the key to avoid vocal cord palsy and it is necessary for intermittent nerve stimulations during conventional IONM. Selective use of IONM during high-risk thyroidectomy decreases the rate of RLN palsy and should be recommended during re-operation or thyroidectomy for malignancy.

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Legend:

Fig. 1 PRISMA Flowchart of article selection

Fig. 2 Forest plot showing the rate of (A) overall, (B) permanent and (C) temporary recurrent laryngeal nerve palsy in visualization alone (VA) group and intra-operative neuro-monitoring (IONM) group during overall high risk thyroidectomy. Abbreviation: VA = visualization alone; IONM = intra-operative neuro-monitoring; RLN = recurrent laryngeal nerve

Fig. 3 Forest plot showing the rate of (A) overall, (B) permanent and (C) temporary recurrent laryngeal nerve palsy in visualization alone (VA) group and intra-operative neuro-monitoring (IONM) group during re-operation thyroidectomy

Abbreviation: VA = visualization alone; IONM = intra-operative neuro-monitoring; RLN = recurrent laryngeal nerve

Fig. 4 Forest plot showing the rate of (A) overall, (B) permanent and (C) temporary recurrent laryngeal nerve palsy in visualization alone (VA) group and intra-operative neuro-monitoring (IONM) group during thyroidectomy for malignancy

Abbreviation: VA = visualization alone; IONM = intra-operative neuro-monitoring; RLN = recurrent laryngeal nerve

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Table 1. Comparison of study design, distribution of high-risk subgroup, quality of study and number of nerves-at-risk in ten included studies.

Author	Year	Country	Type of study	High risk subgroup				NOS			Nerves at risk	
				Re-operation	Mali-gnancy	Thyro-toxicosis	Retro-sternal	Selection	Comparability	Outcome	VA	IONM
Dralle[6]	2004	Germany	PCS, MC	√	√	√		****	*	**	1128	3138
Yarbrough[21]	2004	United States	RS	√				***		*	79	72
Chan[16]	2006	Hong Kong	PCS	√	√	√	√	****	*	**	293	301
Atallah[22]	2009	France	RS	√	√	√	√	**	*	**	240	181
Frattini[17]	2010	Italy	RS		√			***	*	***	152	152
Barczynski[18]	2011	Poland	RS		√			**	*	***	302	302
Alesina[17]	2012	Germany	RS	√				***	*	**	161	128
Alesina[23]	2013	Greece	RS	√				***	*		61	60
Barczynski[14]	2014	Poland	RS	√				***	*	**	826	500
Prokopakis[24]	2014	Italy	RS		√	√		****	*	*	1218	1321

Abbreviation: NOS Scale = Newcastle-Ottawa Scale, PCS = Prospective comparative study; RS = Retrospective comparative study; MC = multi-center study; VA = visualization of recurrent laryngeal nerve alone, IONM = intra-operative neuro-monitoring

Table 2. Initial post-operative laryngoscopic assessment, definition of permanent recurrent laryngeal nerve palsy, set-up and application of intra-operative neuro-monitoring (IONM).

Author	Initial post-operative assessment		Definition of permanent palsy	IONM Set-up			Application of IONM	
	Timing	Method		Electrode	Machine	Stimulation	Site of stimulation	Pre-dissection vagal stimulation
Dralle[6]	-	Laryngoscopy	6 months	NE	Neurosign 100	0.05-5mA	RLN	-
Yarbrough[21]	-	IL / FL	-	NE	-	-	RLN, vagus	-
Chan[16]	< 2 weeks	IL / FL	12 months	SE	Neurosign 100	0.5-1.5mA	RLN	-
Atallah[22]	< 1 week	DL / FL	12 months	SE	NIMS 2.0	0.4-1.5mA	RLN, vagus	-
Frattini[17]	1-2 days	Laryngoscopy	12 months	-	NIMS 2.0	0.5-3 mA	RLN, vagus	Yes
Barczynski[18]	At the end of operation	RL	12 months	NE	Neurosign 100	1mA	RLN, vagus	Yes
				SE	NIMS 2.0	1mA		
Alesina[23]	1 day	DL	6 months	Before 2009, NE	Neurosign	-	RLN, vagus	-
				After 2010, SE	NIMS 3.0	0.5-1.0mA		
Prokopakis[24]	-	FL	#	SE	NIMS	0.5mA	RLN	-
Barczynski[20]	1 day	IL / DL	12 months	In 2004-2007, NE	Neurosign 100	1mA	RLN, vagus	Yes
				In 2008-2012, SE	NIMS 2.0/3.0	1mA		
Calo[32]	2 day	Laryngoscopy	12 months	SE	NIMS 2.0/3.0	-	RLN, vagus	Yes

Abbreviation: RLN = recurrent laryngeal nerve; RL = rigid laryngoscopy; DL = direct laryngoscopy; IL = indirect laryngoscopy; FL = flexible laryngoscopy; IONM = intra-operative neuro-monitoring; SE = surface electrode at endotracheal tube; NE = needle electrode

- All patients with RLN palsy recovered within 4 months

Table 3. Power calculation of minimal number of nerves-at-risk (NARs) to demonstrate significant difference between visualization alone (VA group) and intra-operative neuro-monitoring (IONM group).

	Rate of RLN palsy			**Minimal number of NARs for each group**	**NARs in this study**	
	VA	**IONM**	**OR**		**VA**	**IONM**
Overall high risk						
Overall palsy	4.5%	2.5%	1.40*	4962	4460 (89.9%)	6155 (124.0%)
Permanent palsy	1.6%	1.3%	1.33	12960	4399 (33.9%)	6095 (47.0%)
Temporary palsy	3.9%	2.4%	1.47*	4711	3332 (70.7%)	3017 (64.0%)
Re-operation						
Overall palsy	7.6%	4.5%	1.32*	4196	1497 (35.7%)	1751 (41.7%)
Permanent palsy	2.7%	2.5%	1.40	4744	1436 (30.6%)	1691 (35.6%)
Temporary palsy	6.3%	4.3%	1.24	7561	1188 (15.7%)	812 (10.7%)
Malignancy						
Overall palsy	3.5%	2.1%	1.52^	3552	1596 (44.9%)	2468 (69.5%)
Permanent palsy	1.2%	1.3%	1.13	77499	1596 (2.1%)	2468 (3.2%)
Temporary palsy	3.1%	1.6%	1.90*	1764	1160 (65.8%)	1282 (72.7%)
Thyrotoxicosis						
Overall palsy	1.1%	0.65%	1.33	26190	1166 (4.5%)	1836 (7.0%)
Permanent palsy	0.6%	0.2%	3.56^^	3353	1166 (34.8%)	1836 (54.8%)
Temporary palsy	0.8%	1.2%	0.60	48103	751 (1.6%)	727 (1.5%)

Abbreviation:

NAR = nerve-at-risk, VA = visualization alone; IONM = intra-operative neuro-monitoring; RLN = recurrent laryngeal nerve; OR = odd ratio

* - p-value < 0.05; ^ - p-value = 0.050; ^^ - p-value = 0.051

Reference:

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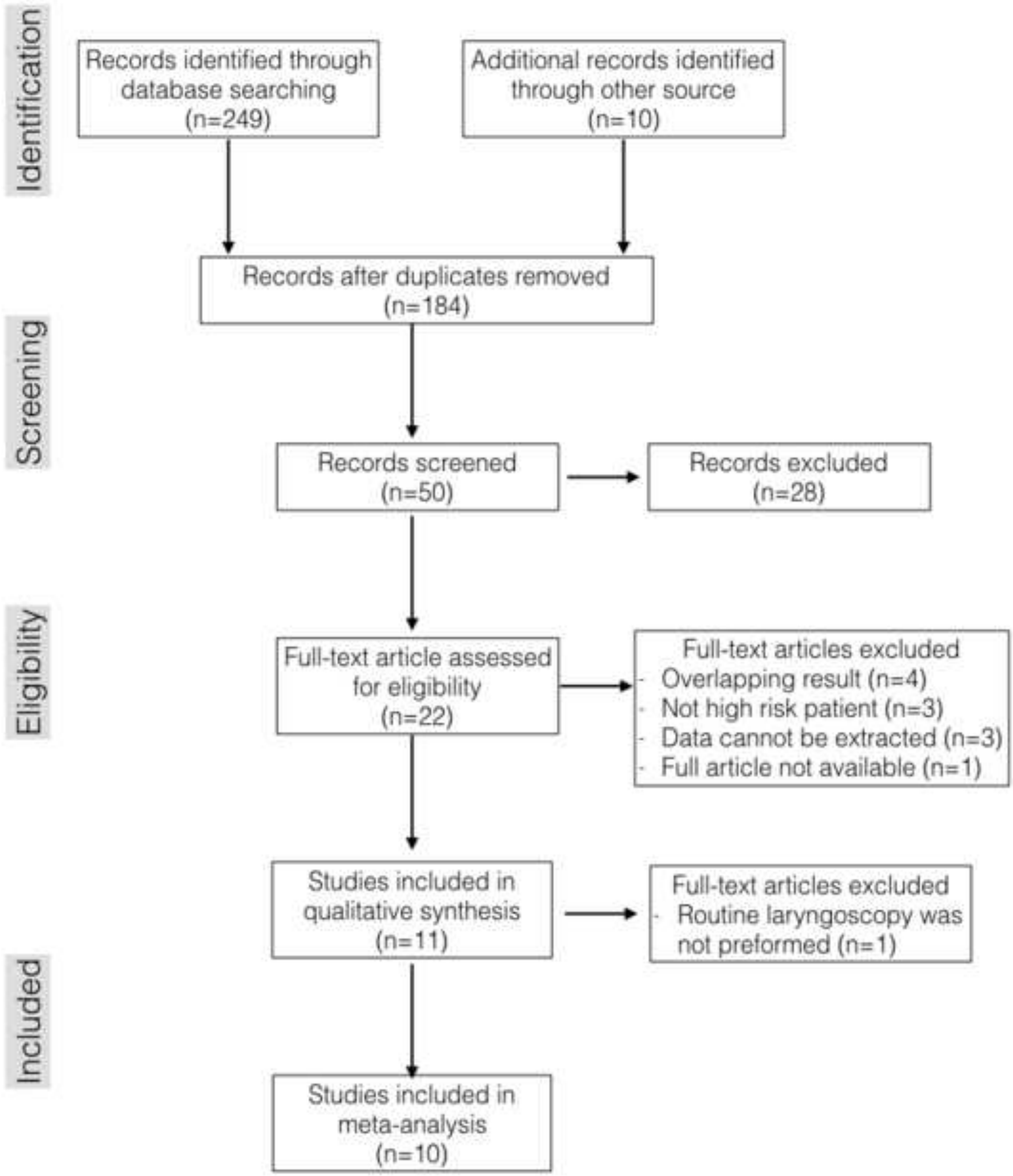

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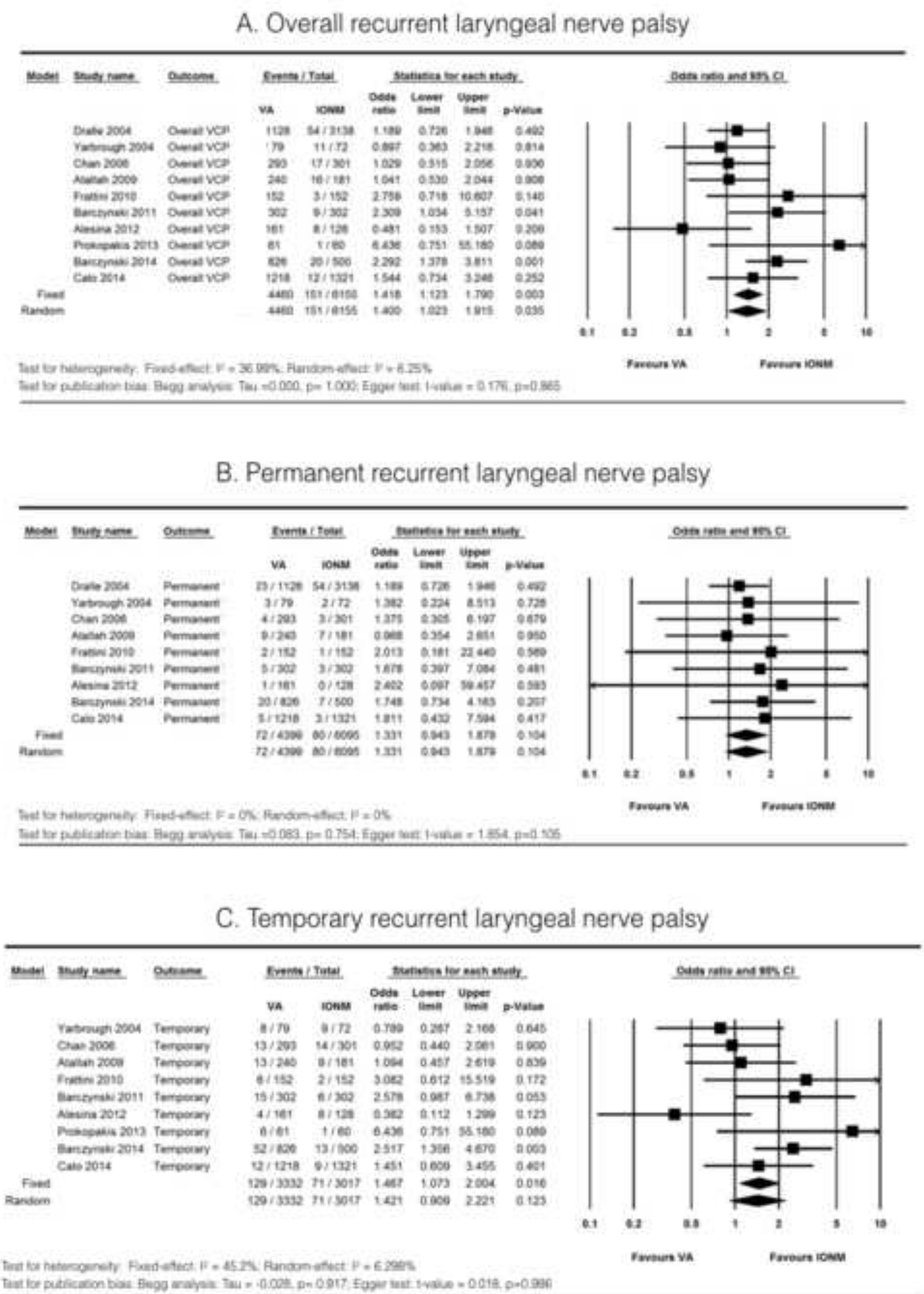

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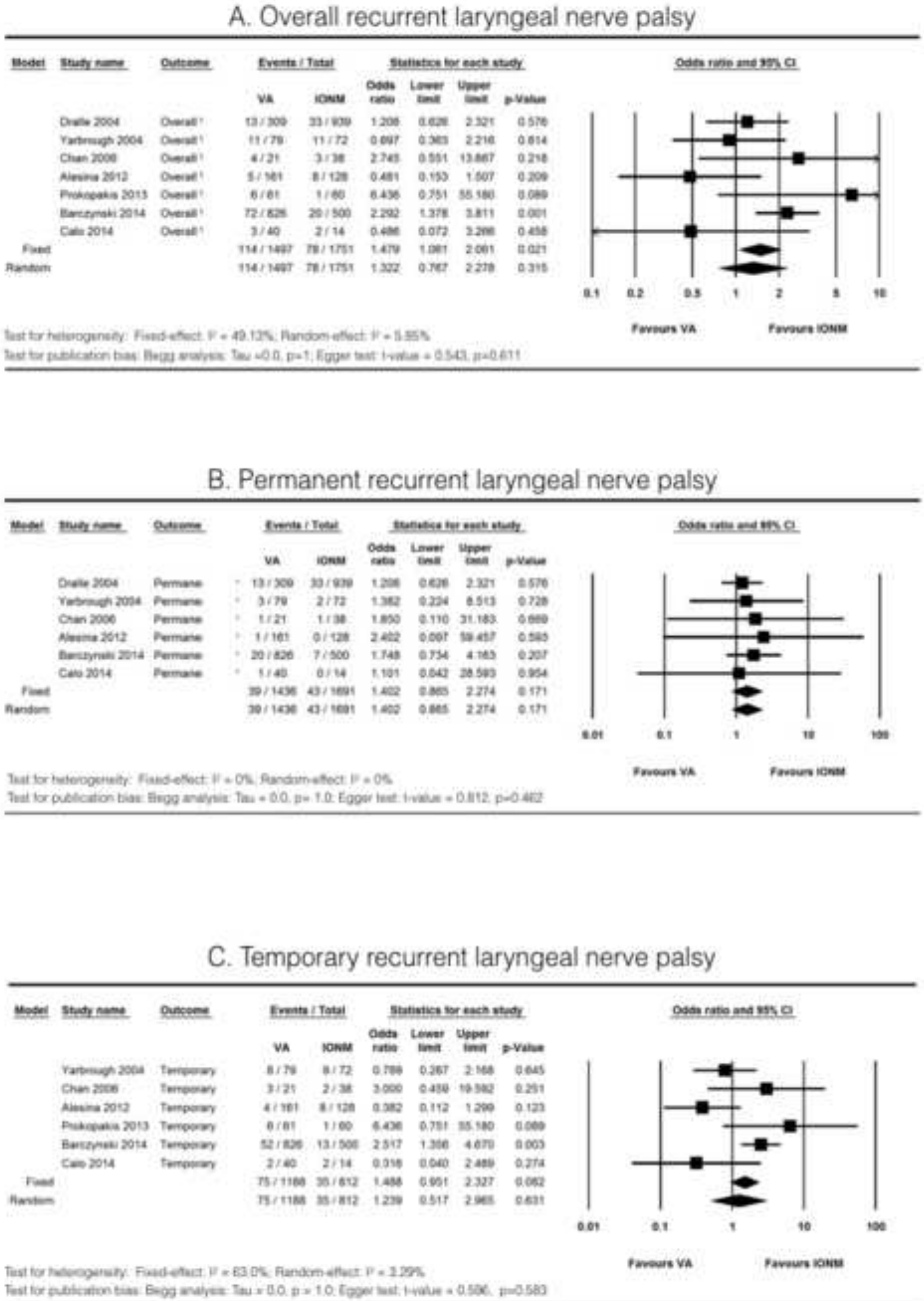

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