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Review Article

Intraoperative recurrent laryngeal nerve monitoring versus visualisation alone - A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Intraoperative nerve monitoring (IONM) is perceived to reduce recurrent laryngeal nerve injury (RLNI) compared to RLN visualisation alone (VA). We performed a meta-analysis of randomized controlled trials (RCTs) to establish the value of using IONM instead of RLN VA for patients undergoing thyroidectomy.

Methods: A meta-analysis of RCTs was performed as per PRISMA guidelines. RLNI rates were expressed as dichotomous variables and pooled as odds ratios (OR) and associated 95% confidence intervals (CI) using the Mantel–Haenszel method.

Results: Eight RCTs with 2521 patients with 4977 nerves at risk were included. Overall, 49.8% of RLNs underwent IONM (2480/4978) and 50.2% underwent VA (2497/4978). Overall RLNI rates were higher for VA (VA: 3.2% (80/2497) vs. IONM: 2.3% (58/2480), OR: 0.72, 95% CI: 0.51–1.02, $P = 0.060$, $I^2 = 9\%$). Permanent RLNI rates were slightly higher for VA (VA: 0.6%, (12/2497) vs. IONM: 0.5%, (12/2480), OR: 0.76, 95% CI: 0.36–1.59, $P = 0.470$, $I^2 = 0\%$).

Conclusion: When compared to VA alone, using IONM failed to significantly reduce RLNI rates during thyroid surgery.

1. Introduction

Since the era of Theodor Kocher,[1] the identification and preservation of recurrent laryngeal nerves (RLNs) during thyroid surgery has been paramount in successfully preventing recurrent laryngeal nerve injury (RLNI). Traditionally, avoiding damage to the RLN was solely dependent upon nerve visualisation with extensive knowledge of typical and variant nerve anatomy (or visualisation alone (VA)). In the late 1960's,[2] intraoperative nerve monitoring (IONM) made its debut in thyroid surgery and has since become increasingly popular in reducing iatrogenic RLNI. IONM systems use electromyography of the vocal cords to monitor the electrophysiological activity of the RLNs.[3] This method of neuromonitoring can be performed intermittently through ipsilateral stimulation of the RLN using a handheld monopolar or bipolar probe,[4] or continuously by ipsilateral vagal nerve stimulation via clip electrodes mounted upon the vagus nerve.[5,6] At present, data from Europe and the United States suggests that 93%–98% of head and neck and endocrine surgeons routinely use either form of IONM to confirm location of the RLN during surgery.[7,8] While there is a recent trend favouring robust IONM utilisation to identify and establish the integrity of the RLNs, uptake of continuous IONM has been modest, with intermittent IONM still being used in greater than 80.0% of European facilities.[8] In spite of intermittent neuromonitoring having strong sensitivity in accurately detecting nerve function, this method is subject to the major limitation of being only useful once RLNI has occurred and is poor in detecting impending injury.[9]

In spite of the widespread adoption of IONM into clinical surgical practice, there remains inconsistencies in the data supporting IONM use in preventing RLNI. Several previous meta-analyses have been performed with the intention of evaluating the clinical utility of IONM in facilitating RLN integrity during thyroidectomy,[10–16] some of which conclude that the increasing availability of neuromonitoring is advantageous in reducing RLNI and support its use as routine in thyroid surgery.[13–16] Conversely, other meta-analyses have successfully challenged this perception,[10,11] with others outlining the added complexity of IONM in the perioperative setting.[17] For example, in their meta-analysis of 23,512 patients and 35,513 nerves at risk (NAR), Pisanu et al. demonstrated no advantage of using IONM in reducing RLNI compared

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to VA (RLNI rate: 3.47% in IONM vs. 3.67% in VA).[10] Additionally, Page et al. observed an increase in permanent RLNI rates in a prospective observational study of 767 patients over a 10-year period (IONM: 2.0% (6/306) vs. VA: 1.3 (6/461)).[18] Therefore, the added value of routine intermittent IONM use over VA may be brought into question for reducing RLNI rates.

None of these previous meta-analyses have established the value of IONM in RLN preservation in the setting of randomized controlled trial (RCT) data only. Accordingly, the aim of the current study was to perform a systematic review and meta-analysis of RCTs to establish the 'real world' value of using IONM instead of RLN VA for patients undergoing thyroidectomy. Our hypothesis was that there would be a reduction in RLNI rates when IONM methodology was employed.

2. Methods

This systematic review and meta-analysis was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[19,20] All authors contributed to formulating the study protocol and it was then registered with the International Prospective Register of Systematic Reviews (PROSPERO). Institutional review board ethical approval was not required.

2.1. Population, Intervention, Comparison, and outcomes (PICO)

Using the PICO framework,[21] the aspects the authors wished to address were:

Population – Patients indicated to undergo thyroid surgery aged 18 years or older with no known impairment of either RLN confirmed with laryngoscopy prior to surgery who are recruited to an RCT comparing IONM and VA as a means to prevent RLNI.

Intervention – Any patient in the selected group who had their RLN identified using IONM.

Comparison – Any patient in the selected group who had their RLN identified using VA alone.

Outcomes – Primary outcomes included: (1) Overall RLNI rates for IONM and VA.

Secondary outcomes included: (1) Transient RLNI rates for IONM and VA, and (2) Permanent RLNI rates for IONM and VA.

2.2. Study eligibility

To be included in the current analysis, studies had to fulfil the following criteria: Included studies had to have a clear research methodology, including the prospective randomisation of patients to IONM and VA during thyroid surgery and report on the primary outcome measure (overall RLNI rates following thyroid surgery). All studies had to have a full-text available. Studies were excluded if they failed to meet the above inclusion criteria.

2.3. Search strategy

An electronic search for relevant studies was performed of the *PubMed, Embase and Cochrane Central Register of Controlled Trials* databases for relevant studies. The final search was performed on the 30th October 2021. This search was performed by two independent reviewers (MGD and EFC), using a predetermined search strategy that was designed by the senior authors. This search included the search terms: (thyroidectomy) and (nerve monitoring or nerve stimulation) and (RLN or recurrent laryngeal nerve or vagus or vocal cord), which were linked with Boolean operators, 'AND' and 'OR'. Included studies were limited to RCTs published in the English language and were not restricted by year of publication. All duplicate studies were manually removed, before titles were screened, and studies considered appropriate had their abstracts and/or full text reviewed. Retrieved studies were reviewed to ensure inclusion criteria were met for one primary and secondary outcome at a minimum. In cases of discrepancies of opinion, a third author was asked to arbitrate (AJL).

2.4. Data extraction and quality assessment

The following data was extracted and collated from retrieved studies meeting inclusion criteria: (1 First author name, (2) year of publication, (3) study design, (4) country of origin, (5) number of patients, (6) mean age, (7) clinicopathological and surgical data, (8) number of NAR, (9) nerve monitoring device used in cases of IONM, (10) primary outcomes measures (i.e.: overall RLNI rate), and (11) secondary outcomes measures (i.e.: transient and permanent RLNI rates). Risk of bias and quality assessment of included studies was performed by two independent reviewers using the revised Cochrane risk-of-bias tool for randomized trials[22] and Jadad scale.[23] In cases of discordance of opinion, a third author was asked to arbitrate.

2.5. Definitions

- RLNI was defined as 'confirmed ipsilateral RLN paresis confirmed on post-operative laryngoscopic examination following thyroid surgery', as outlined previously by Barczynski et al.[24]
- Transient RLNI was defined as 'RLNI which resolved within 6-months of thyroid surgery', while permanent RLNI included 'RLNI unresolved 6-months or longer after surgery'.[25,26]
- IONM was defined as any method (including intermittent or continuous IONM) involving electro-myographic monitoring of the RLN during surgery, which provides feedback in real-time to the resecting surgeons, with the intention of preserving the RLN integrity.[27]

2.6. Statistical analysis

Descriptive statistics were used to determine the associations of nerve monitoring techniques and the proportion of RLNI rates (Fisher's Exact Test, †).[28] Thereafter, overall, transient, and permanent RLNI rates were expressed as dichotomous or binary outcomes, reported as odds ratios (ORs) were expressed with 95% confidence intervals (CIs) following estimation using the Mantel-Haenszel method. ORs were calculated, using crude event RCT data, to compare interventions using per-protocol data, where applicable. Either fixed or random effects models were applied on the basis of whether significant heterogeneity (I^2 >50%) existed between studies included in the analysis. Symmetry funnel plots were used to assess publication bias. Statistical heterogeneity was determined using I^2 statistics. All tests of significance were two-tailed with $P < 0.050$ indicating statistical significance. Descriptive statistics were performed using the Statistical Package for Social Sciences (SPSS) version 26 (International Business Machines Corporation, Armonk, New York). Meta-analysis was performed using Review Manager (RevMan), Version 5.4 (Nordic Cochrane Centre, Copenhagen, Denmark).

3. Results

3.1. Literature search and study characteristics

The systematic search strategy identified a total of 973 studies, of which 84 duplicate studies were manually removed. The remaining 889 studies were screened for relevance, before 43 full texts were reviewed. In total, 8 RCTs met our eligibility criteria and were included in this systematic review and meta-analysis[24,29–35] (Fig. 1). Of the 8 RCTs included in this analysis, all studies reported outcomes in relation to intermittent IONM compared to VA (100.0%, 8/8) and 75.0% were conducted in European surgical research institutions (6/8).[24,29–31,34,35] Publication dates ranged from 2009 to 2021. Study data and risk of bias

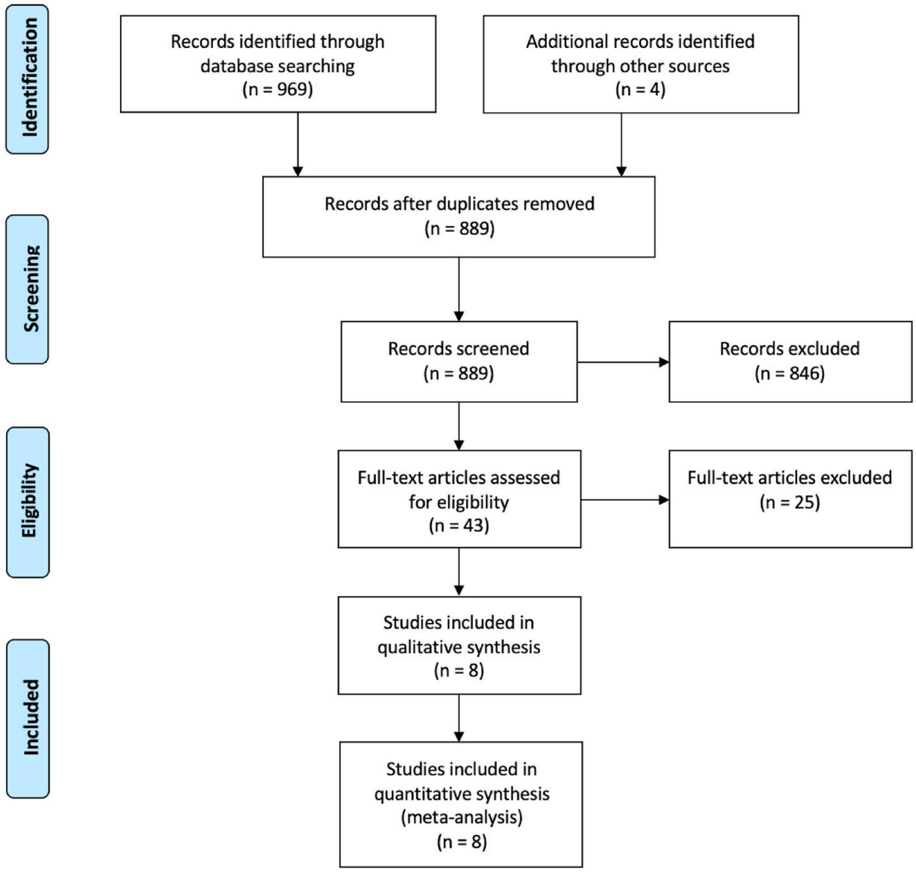

Fig. 1. PRISMA flow diagram detailing the systematic search process.

assessments for the 8 included RCTs are outlined in Table 1.

3.2. Clinicopathological and surgical characteristics

In total, there was data included from 2521 patients with 4977 nerves at risk (NAR). The mean age at diagnosis of 48.5 years (range: 18–77 years) and the majority of patients were female (88.9%, 2240/2521). Overall, 79.1% of patients underwent total thyroidectomy (1995/2251). Overall, 49.8% of RLNs underwent IONM (2480/4978) and 50.2% underwent VA (2497/4978) respectively. Available clinicopathological data are outlined in Table 2.

3.3. Recurrent laryngeal nerve injury rates

When analysing data from the 8 included RCTs, the overall RLNI rate was 2.8% (138/4977 NAR). The overall RLNI rates were higher for those who underwent VA compared to those who underwent IONM (VA: 3.2% (80/2497) vs. IONM: 2.3% (58/2480), $P = 0.069$, †) (Table 3). Similarly, this trended towards significance for reducing overall RLNI at meta-analysis (OR: 0.72, 95% CI: 0.51–1.02, $P = 0.060$, $I^2 = 9\%$) (Fig. 2).

Overall, the transient RLNI rate was 1.8% (90/4977 NAR). Transient RLNI rates were higher for those who underwent VA compared to those who underwent IONM (VA: 2.1% (53/2497) vs. IONM: 1.5% (37/2480), $P = 0.110$, †) (Table 3). At meta-analysis, there was no significant difference in transient RLNI rates for VA and IONM (OR: 0.69, 95% CI: 0.42–1.06, $P = 0.090$, $I^2 = 42\%$) (Fig. 3).

The rate of permanent RLNI rate was 0.4% for the entire group (20/4977 NAR). Permanent RLNI rates were slightly higher in those undergoing VA (0.6%, 12/2497) than in those undergoing IONM (0.5%, 12/2480) ($P = 0.571$, †) (Table 3). At meta-analysis, there was no difference in permanent RLNI rates for VA and IONM (OR: 0.76, 95% CI: 0.36–1.59, $P = 0.470$, $I^2 = 0\%$) (Fig. 4).

Table 1
Study data and risk of bias assessments for the 8 included randomised controlled trials.

Author	Year	Study	Country	N	NAR	IONM	VA	RoB2	Jadad
Barczyaski	2012	RCT	Poland	201	402	200	202	Some concerns	5
Barczyaski	2009	RCT	Poland	1000	2000	1000	1000	Low risk	5
Dionigi	2009	RCT	Italy	72	224	110	114	Some concerns	4
Ercetin	2019	RCT	Turkey	795	1496	736	760	Some concerns	5
Hei	2015	RCT	China	70	84	41	43	Some concerns	5
Maneeprasopchoke	2021	RCT	Thailand	32	41	21	19	Some concerns	5
Sari	2010	RCT	Turkey	237	409	210	199	Low risk	5
Teksoz	2015	RCT	Turkey	161	322	162	160	Some concerns	4
Total/Median	–	–	–	2521	4978	2480	2497	–	5

N; number, NAR; nerves at risk, IONM; intraoperative nerve monitoring, VA; visualisation only, RoB2; Cochrane risk-of-bias tool for randomised studies, RCT; randomised controlled trial.

Table 2
Available clinicopathological data from each of the 8 included randomised controlled trials.

Author	Year	Male	Female	Mean age in years (range)	Total Thyroidectomy	Thyroid cancer
Barczyaski	2012	0	201	50	201	25
Barczyaski	2009	87	913	51.6	749	122
Dionigi	2009	10	62	40.5 (19–77)	40	40
Ercetin	2019	130	665	47.8	748	0
Hei	2015	16	54	57.5	37	54
Maneeprasopchoke	2021	5	27	43.3 (18–65)	10	20
Sari	2010	42	195	47.7	49	41
Teksoz	2015	38	123	49.5	161	54
Total	–	328	2240	48.5 (18–77)	1995	356

Table 3
Data on recurrent Laryngeal Nerve Injury Rates from each of the 8 included randomised controlled trials.

Author	Year	IONM	Overall RLNI for IONM	Transient RLNI for IONM	Permanent RLNI for IONM	VA	Overall RLNI for VA	Transient RLNI for VA	Permanent RLNI for VA
Barczyaski	2012	200	1	0	1	202	2	0	2
Barczyaski	2009	1000	27	18	9	1000	50	38	12
Dionigi	2009	110	1	1	0	114	3	3	0
Ercetin	2019	736	9	N/R	N/R	760	11	N/R	N/R
Hei	2015	41	7	5	2	43	4	3	1
Maneeprasopchoke	2021	21	0	0	0	19	0	0	0
Sari	2010	210	3	3	0	199	3	3	0
Teksoz	2015	162	10	10	0	160	7	6	1
Total	–	2480	58	37	12	2497	80	53	16
Proportion	–	49.8%	2.3%	1.5%	0.5%	50.2%	3.2%	2.1%	0.6%

IONM; intraoperative nerve monitoring, RLNI; recurrent laryngeal nerve injury, VA; visualisation only, N/R; not reported.

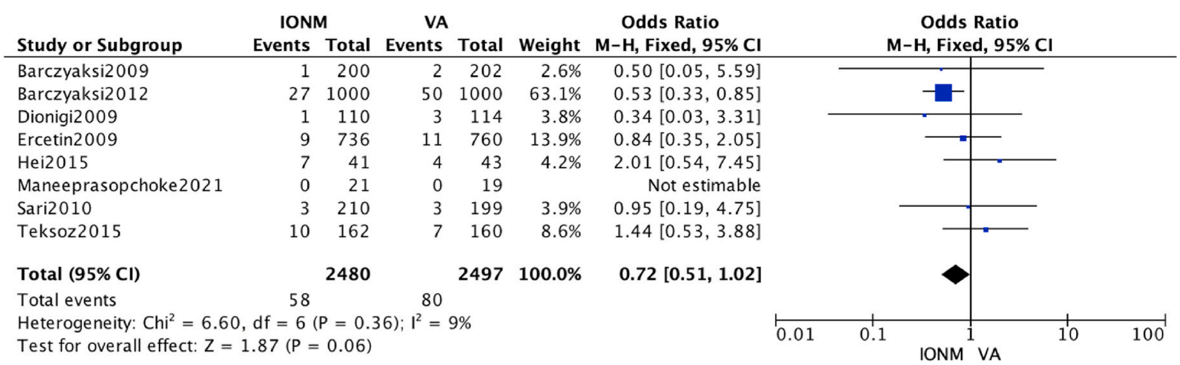

Fig. 2. Forest plot comparing intraoperative nerve monitoring and nerve visualisation alone for overall recurrent laryngeal nerve injury.

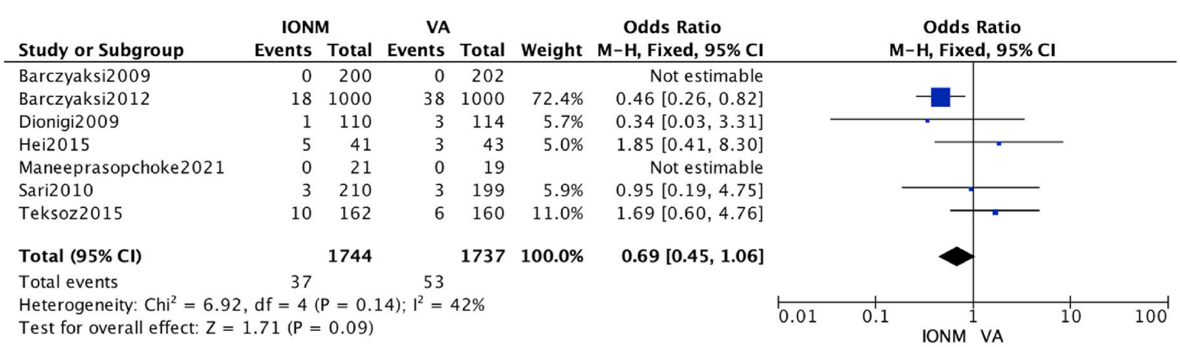

Fig. 3. Forest plot comparing intraoperative nerve monitoring and nerve visualisation alone for transient recurrent laryngeal nerve injury.

4. Discussion

This systematic review and meta-analysis of RCTs demonstrated similar RLNI rates when using IONM compared with VA to aid RLN preservation during thyroid surgery. Overall, the application of IONM during thyroidectomy trended towards significance for preserving overall RLN integrity, while both IONM and VA yielded equivalent results in relation to transient and permanent RLNI rates. While these results failed to achieve statistical significance, these are nevertheless interesting findings: Although IONM failed to achieve statistical significance in reducing RLNI in this meta-analysis (OR: 0.72, 95% CI: 0.51–1.02, $P = 0.060$, $I^2 = 9\%$), the crude results of this study outline the

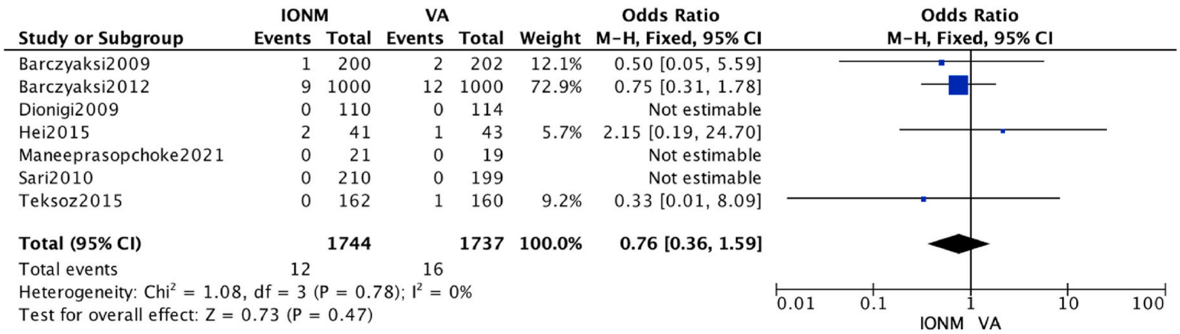

Fig. 4. Forest plot comparing intraoperative nerve monitoring and nerve visualisation alone for permanent recurrent laryngeal nerve injury.

slight clinical advantage of routine neuromonitoring during thyroidectomy (RLNI rates for VA were 3.2% (80/2497) vs. 2.3% (58/2480) for IONM, with an absolute reduction in overall RLNI by 1% (therefore sparing 1 in every 100 patients undergoing thyroid surgery RLNI as a complication). Additionally, this analysis demonstrated a relative reduction of over 25% in RLNI rates when using IONM, indicating one of every four patients who succumb to RLNI using VA may be spared nerve impairment if IONM is employed by their surgeons. These are important findings that coincide with the previous expert consensus statements delivered by the German Association of Endocrine Surgeons,[36] Australian College of Surgeons,[37] and International Intraoperative Neural Monitoring Study Group,[27] all of whom advocate for IONM and RLN visualisation during thyroidectomy to achieve the best clinical outcomes. Therefore, this study adds further clarity and insights to the best practice of RLN management for the thyroid surgeon.

In this meta-analysis, subgroup analyses for RLNI rates for transient and permanent RLNI were similar for both IONM and VA RLN preservation methods. Given the results slightly in favour IONM improving RLNI rates for the overall cohort, these results may be perceived to be somewhat surprising: For assessment of transient and permanent RLNI rates independently, there was a reduced number of events in each group compared to the overall RLNI rate (n = 138 for overall, n = 90 for transient, and n = 28 for permanent respectively). The small number of RLNI events in each group potentially contribute to a potential underestimation of the reported significance or impact of IONM on RLNI, particularly when compared to the potential benefit at a population level. Moreover, it must be acknowledged that the generally low incidence of RLNI limits the possibilities performing prospective, randomized studies proving or disproving the utility of novel measures which may impact RLNI rates (such as IONM), as is evident in this meta-analysis where the two smallest RCTs have limited impact on the results observed.[32,33] Accordingly, systematic review and meta-analysis methodology is likely the best platform to evaluate this research question, as is evident through the efforts of previous authors to establish the value of IONM for thyroid surgery.[10,11,13–16]

Interestingly, the overall RLNI rate for all NAR in this study was 2.8% (138/4977), which is significantly lower than data reported by previous authors in the era prior to neuromonitoring (overall RLNI rates of: 3.4%–5.9%).[38,39] This indirectly suggests more cautious surgical management of the RLN is in vogue in recent years, which is replicated through the extensive research in recent decades, as there has been several systematic review and meta-analyses performed addressing this conundrum, including a systematic review of the previous meta-analyses performed.[12] In 2013, Sanabria et al. conducted a meta-analysis of 6 RCTs with 1602 patients and 3064 NAR evaluating the value of IONM on injury to RLN or the external branch of the superior laryngeal nerve (EBSLN) which failed to demonstrate a significant reduction in nerve injury using IONM.[13] This is the only previous meta-analysis of RCT data only evaluating nerve palsy rates using IONM albeit limited due to the inclusion of results for EBSLN. Nonetheless, the results from Sanabria et al. identify the value of IONM despite its failure to achieve statistical significance, which correlate directly with the results of the current study. Yang et al. performed a meta-analysis of 23 studies (including 4 RCTs, 6 prospective studies, and 13 retrospective studies) which included 9203 patients undergoing thyroid surgery and 17,203 NAR.[14] Interestingly, when focusing solely on RLNI and including more moderate levels of evidence, IONM successfully reduced overall (OR: 0.81, 95% CI: 0.66–0.99) and transient (OR: 0.76, 95% CI: 0.61–0.94) RLNI rates respectively, when compared to Sanabria et al.[13] Wong et al. performed a meta-analysis which established the protective role of IONM for overall (VA: 4.5% vs. IONM: 2.5%, OR: 1.40, 95% CI: 1.12–1.79) and transient (VA: 3.9% vs. IONM: 2.4%, OR: 1.47, 95% CI: 1.07–2.00) RLNI for patients undergoing 'high-risk' thyroidectomy.[15] Similarly, Bai et al. performed a large meta-analysis of 34 non-randomized studies which reinforced the results presented by Wong et al. supporting IONM in reducing RLNI (overall RLNI: OR: 0.68, 95% CI: 0.55–0.83, transient RLNI: OR: 0.71, 95% CI: 0.57–0.88).[16] As previously described, Pisanu et al. performed a meta-analysis of 23,512 patients and 35,513 NAR which yielded results failing to provide statistical evidence to support the routine use of IONM to reduce RLNI.[10] Finally, Malik et al. reported congruent results to the aforementioned authors in their large meta-analysis of 30,926 patients (overall RLNI: IONM 3.2% vs. VA 3.8%).[11]

Despite several strengths, the authors acknowledge certain unavoidable limitations to this meta-analysis of RCTs. As previously outlined, clinical studies evaluating the role of IONM on RLNI rates are inherently limited due to a large number of patients being required to be treated, before significant differences are observed in the incidence rates of RLNI. This ultimately limits the value of small prospective, randomized studies successfully proving or disproving the utility of IONM in impacting RLNI rates. Conversely, this does support the use of meta-analysis methodology in the procurement of definitive conclusions in relation to neuromonitoring of the RLN intraoperatively. Secondly, in this study, data included from Barczayski et al. comprised 63.1%, 72.4%, and 72.9% of all data integrated at meta-analysis with respect to overall, transient, and permanent RLNI, inevitably influencing the results obtained, which inevitably skews results in favour of this large RCT with 2000 recruited patients.[24] Thirdly, as may be disputed with a large proportion of RCTs in the field of surgery, it is extremely challenging to fully 'blind' surgeons from interventions such as IONM. This inevitably and uncontrollably makes these RCTs 'open label' trials, rendering them subject to unintentional biases.[40] Additionally, surgeon experience has the strong potential to confound RLNI rates and has not been established in this meta-analysis. Lastly, despite the seminal work of Schneider et al. implicating continuous IONM as being clinically advantageous over conventional intermittent IONM to reduce RLNI rates, none of the available RCTs assessed the value of continuous IONM compared to VA.[6] Therefore, it is plausible to suggest RLNI rates may improve if continuous neuromonitoring methodology is employed in prospective RCTs. In spite of these shortcomings, this meta-analysis of RCTs provides comprehensive analyses of available RCT data comparing IONM and RLN VA during thyroid surgery.

The current systematic review and meta-analysis is the largest study using RCT data only to determine the value of intraoperative neuromonitoring of RLNI rates during thyroid surgery. The crude data from this study outline the trivial role of IONM in reducing overall, transient, and permanent RLNI rates, therefore not advocating for its utility as routine. Moreover, IONM only demonstrated a relative reduction of approximately 25% in overall RLNI when neuromonitoring methodology is applied, which failed to achieve statistical significance. Therefore, IONM does not seem to be useful in significantly reducing RLNI rates. The next generation of phase III, randomized studies may interrogate these findings and decipher the optimal strategy for RLN monitoring as the paradigm evolves to establish whether there is a benefit from using intermittent or continuous IONM over VA in those undergoing thyroid surgery.

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Declaration of competing interest

None of the authors having any conflicts of interest to disclose.

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