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Systematic review with meta-analysis of studies comparing intraoperative neuromonitoring of recurrent laryngeal nerves *versus* visualization alone during thyroidectomy

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ABSTRACT

Background: The role of intraoperative neuromonitoring (IONM) of the recurrent laryngeal nerve (RLN) during thyroid surgery is still debatable. The aim of this meta-analysis was to evaluate the potential improvement of IONM *versus* RLN visualization alone (VA) in reducing the incidence of vocal cord palsy.

Methods: A literature search for studies comparing IONM *versus* VA during thyroidectomy was performed. Studies were reviewed for primary outcome measures: overall, transient, and permanent RLN palsy per nerve and per patients at risk; and for secondary outcome measures: operative time; overall, transient and permanent RLN palsy per nerve at low and high risk; and the results regarding assistance in RLN identification before visualization.

Results: Twenty studies comparing thyroidectomy with and without IONM were reviewed: three prospective, randomized trials, seven prospective trials, and ten retrospective, observational studies. Overall, 23,512 patients were included, with thyroidectomy performed using IONM compared with thyroidectomy by VA. The total number of nerves at risk was 35,513, with 24,038 nerves (67.7%) in the IONM group, compared with 11,475 nerves (32.3%) in the VA group. The rates of overall RLN palsy per nerve at risk were 3.47% in the IONM group and 3.67% in the VA group. The rates of transient RLN palsy per nerve at risk were 2.62% in the IONM group and 2.72% in the VA group. The rates of permanent RLN palsy per nerve at risk were 0.79% in the IONM group and 0.92% and in the VA group. None of these differences were statistically significant, and no other differences were found.

Conclusions: The current review with meta-analysis showed no statistically significant difference in the incidence of RLN palsy when using IONM *versus* VA during thyroidectomy. However, these results must be approached with caution, as they were mainly based on data coming from non–randomized observational studies. Further studies including high-quality multicenter, prospective, randomized trials based on strict criteria of standardization and subsequent clustered meta-analysis are required to verify the outcomes of interest.

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1. Introduction

Routine recurrent laryngeal nerve (RLN) visualization is considered the current gold standard of care for the prevention of nerve injury and the reduction of nerve palsy during thyroid surgery [1–5]. Despite meticulous anatomical identification, however, RLN injury still exists, with the incidence of transient RLN palsy reported as 0.4%–12%, and permanent RLN palsy up to 5%–6% [6–12].

When nerves are at high risk, such as in thyroidectomies performed for substernal goiter, recurrent goiter, and advanced thyroid carcinoma, RLN palsy can occur even in experienced hands [7,13]. Impaired RLN function causes disability and reduced quality of life, and it is one of the leading reasons for malpractice litigation [14,15]. Thus, intraoperative neuromonitoring (IONM) has been proposed to reduce this complication by preventing RLN injuries and to aid in nerve localization before visualization [16,17].

Some authors have shown that neuromonitoring reduces the rate of transient RLN palsy [7], is useful in the case of thyroid reoperation [4], and can assist in the identification of the RLN during dissection before visualization [7,18,19]. However, the utility of neuromonitoring in decreasing the rate of permanent RLN palsy has not been proven yet [6,20,21].

The recent standardization of neuromonitoring methods and reporting was undertaken in an effort to provide uniformity and to minimize inappropriate variations in the application of IONM [22]. However, the role of IONM during thyroid surgery is still debatable, as no consensus exists regarding the prevention of RLN injury.

Thus far, only two reviews with pooled analysis have been performed to compare the results of IONM of RLN *versus* visualization alone (VA) during thyroidectomy [23,24]. This dearth of research and the need for updated data on the comparison between the two techniques encouraged us to perform this new systematic review with meta-analysis, including the largest number of adult patients from all comparative studies in the literature. The aim of our research was to evaluate whether the use of IONM shows real benefits over VA, especially in terms of reducing the incidence of vocal cord palsy after thyroid surgery.

2. Materials and methods

To be included in our analysis, studies had to meet the following criteria: compare the characteristics and perioperative outcomes of adult patients undergoing thyroidectomy with IONM *versus* VA of the RLN; prospective, randomized clinical trial (RCT) or prospective or retrospective observational study comparing the two techniques; and written in English.

Studies were not included in the meta-analysis if the outcomes of interest (as specified in the following section) were impossible to calculate, or if the standard deviation and confidence interval of the tested parameters were not reported.

A systematic literature search was performed using the Embase, Medline, Cochrane, PubMed, and Google Scholar databases for studies comparing IONM *versus* VA of RLN during thyroidectomy by using the following keywords: thyroidectomy; "RLN"; "IONM"; RLN visualization or "VA"; and RLN palsy. The search was extended using the "related article" function of the databases and by scanning the references of all relevant articles. The literature search was completed in August 2013.

Two authors (AP and GP) independently extracted the following data from each study: institution and year of publication, study type, number of patients operated on with each technique, number of nerves at risk, characteristics of patients such as age and gender, perioperative outcome, and postoperative results.

All included studies were reviewed for the following outcomes of interest:

- The primary outcome measures were rate of overall, transient, and permanent RLN palsy per nerve at risk and rate of overall, transient, and permanent RLN palsy per patient at risk
- The secondary outcome measures were operative time; overall, transient, and permanent RLN palsy per nerve at low and high risk; and results regarding assistance in RLN identification before visualization.

A laryngoscopy to check vocal cord status was performed preoperatively and postoperatively in all included studies. Patients were considered to have permanent RLN palsy if the impaired function persisted at least 6 or 12 m after thyroidectomy, depending on the author's postoperative protocol.

2.1. *Statistical analysis, synthesis, and reporting of results*

The meta-analysis was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [25] and the Meta-Analysis of Observational Studies in Epidemiology checklist for observational studies [26]. Variables were considered for pooled analysis if they were evaluated by two or more studies. All statistical analyses were carried out using MedCalc 2011 (version 11.5.1; MedCalc Software, Ostend, Belgium) statistical software. The meta-analysis was conducted by searching for a numerical estimate of the outcomes of interest, as described elsewhere [27]. For continuous outcomes, Hedges's g statistic was used to calculate the standardized mean difference (SMD) under the fixed effects model, which was adjusted for small sample bias. Under the fixed effects model, it was assumed that all studies were homogenous. This assumption was tested by the heterogeneity test, which was included to calculate the summary SMD under the random effects model, according to the method of DerSimonian and Laird [28]. We tested for heterogeneity using the random effects model to calculate the Q-test and its associated P values. If this test yielded a P value <0.05, then the fixed effects model was considered invalid, and the random effects model was considered appropriate. The results of the individual studies were listed, and the total SMD with 95% confidence interval (CI) were given for both the fixed effects model and the random effects model. If the value 0 was not within the 95% CI, then the SMD was considered statistically significant at the 5% level ($P < 0.05$) (http://www.medcalc.org/manual/meta-continuous.php). This method required the standard deviations and the CIs

of the tested parameters. Studies that did not report any of these parameters were excluded from the meta-analysis. The results of the different studies, with 95% CI and overall SMD, were summarized and reported using a forest plot.

For data derived from contingency tables (qualitative outcomes), we calculated the odds ratio (OR) and 95% CI. The ORs reported in the results are of the pooled analysis method, also called pooled ORs. The Mantel–Haenszel method was used for calculating the weighted summary OR under the fixed effects model. Then, the heterogeneity test was incorporated to calculate the summary OR under the random effects model according to the method of DerSimonian and Laird [28]. If this test yielded a P value <0.05, then the fixed effects model was considered invalid, and the random effects model was considered appropriate. The results of the individual studies were listed and the total OR with 95% CI were given for both the fixed effects model and the random effects model. If the value 1 was not within the 95% CI, then the OR was considered statistically significant at the 5% level ($P < 0.05$) (http://www.medcalc.org/manual/meta-oddsratio.php). The results of different studies, with 95% CI and the overall effect (summary OR) with 95% CI, were summarized on a logarithmic scale using a forest plot.

3. Results

The flowchart of the systematic review is shown in Figure 1. Twenty studies comparing thyroidectomy with IONM *versus* VA of RLN were considered suitable for the pooled analysis [1,4,7,9,11–13,16–18,20,21,29–36]. The articles included in the quantitative synthesis were published between 2004 and 2013. Seven studies were conducted in the US, three in Germany, three in Italy, two in France, two in Poland, one in Brazil, one in China, and one in Turkey. These studies included a total of 23,512 patients with thyroidectomy performed using IONM compared with thyroidectomy by VA of RLN. The total number of nerves at risk was 35,513, with 24,038 nerves at risk (67.7%) in the IONM group and 11,475 nerves at risk (32.3%) in the VA group (Tables 1 and 3). In three prospective RCTs, the patients were randomly assigned to either IONM or VA groups [7,11,31]. The other included studies were seven prospective [1,4,9,17,29,33,34] and ten retrospective comparative observational studies [12,13,16,18,20,21,30,32,35,36].

The mean follow-up period was 18 mo (range, 3 mo–11 y), as reported in the included studies [4,9,16,29–31]. Some authors defined RLN palsy as permanent at 6 mo from the time of the operation [1,4,16,31], whereas others defined it as permanent at 12 mo from the time of the operation [9,11,13,21,29,30,35]. The two reviewers were found to be 100% in agreement about the data extracted from the studies. The characteristics of the included studies, demographics of the included patients, and different methods used for IONM of RLN are shown in Tables 1 and 2.

3.1. Primary outcome measures

3.1.1. Overall, transient, and permanent RLN palsy per nerve at risk

The rate of overall RLN palsy per nerve at risk was 0.0347 in the IONM group *versus* 0.0367 in the VA group (24,038 *versus* 11,475 nerves at risk). This difference was not statistically significant (OR = 0.938, 95% CI = 0.828–1.063; no heterogeneity was found for Q = 17.766, $P = 0.471$; Fig. 2, Table 3). The rate of transient RLN palsy per nerve at risk was 0.0262 *versus* 0.0272 in the IONM and VA groups, respectively. However, this difference was not statistically significant (OR = 0.946, 95% CI = 0.817–1.096; no heterogeneity was found for Q = 15.604, $P = 0.552$; Fig. 3, Table 3). The rate of permanent RLN palsy per nerve at risk was 0.0079 *versus* 0.0092 in the IONM and VA groups, respectively, and this difference was also not statistically significant (OR = 0.884, 95% CI = 0.687–1.136; no heterogeneity was found for Q = 2.830, $P = 1.000$; Fig. 4, Table 3).

3.1.2. Overall, transient, and permanent RLN palsy per patient at risk

The number of patients included in the study of Dralle *et al.* [4] was not specified per group of treatment. Thus, the outcomes of this study were impossible to meta-analyze per patients at risk. The pooled analysis of RLN palsy per patient at risk included 3509 patients from the IONM group *versus* 3486 patients from the VA group. The rate of overall RLN palsy per patient at risk was 0.060 in the IONM group *versus* 0.067 in the VA group. This difference was not statistically significant (OR = 0.873, 95% CI = 0.716–1.063; no heterogeneity was found for Q = 20.471, $P = 0.306$; Fig. 5, Table 3). The rate of transient RLN palsy was 0.035 *versus* 0.045 in the IONM and VA groups, respectively. However, this difference was not statistically significant (OR = 0.837, 95% CI = 0.658–1.066; no heterogeneity was found for Q = 17.013, $P = 0.384$; Fig. 6, Table 3). The rate of permanent RLN palsy was 0.012 *versus* 0.015 in the IONM and VA groups, respectively, and this difference was not statistically significant (OR = 0.873, 95% CI = 0.585–1.301; no heterogeneity was found for Q = 3.264, $P = 0.999$; Fig. 7, Table 3).

Overall, six patients had bilateral vocal cord palsy: three patients in the VA group [13,16,21]; one patient in the IONM group [13]; and the group was not specified in the remaining two patients [9,32].

3.2. Secondary outcome measures

3.2.1. Operative time

The meta-analysis of mean operative time was conducted on total thyroidectomies only. Mean operative time from skin incision to skin closure was longer in the IONM group than in the VA group (97.6 *versus* 94.6 min, respectively; SMD = 0.102, 95% CI = −0.227–0.404). This difference was not significant, and heterogeneity was found for Q = 41.738, $P < 0.0001$; Table 2.

3.2.2. Overall, transient, and permanent RLN palsy per nerve at low risk

The meta-analysis of RLN palsy per nerve at low risk was conducted on only two studies that reported the absolute numbers of injuries to nerves considered at low risk [7,9]. Nerves in thyroidectomies for low-volume, non-toxic nodular goiter and solitary thyroid nodules were those considered to be at low risk. The rate of overall RLN palsy per nerve at low risk was 0.023 in the IONM group *versus* 0.036 in the VA group (694 *versus* 714 total nerves at low risk). This difference was not statistically significant (OR = 0.334, 95% CI = 0.066–1.679; heterogeneity was found for Q = 6.122, $P = 0.013$; Table 4). The

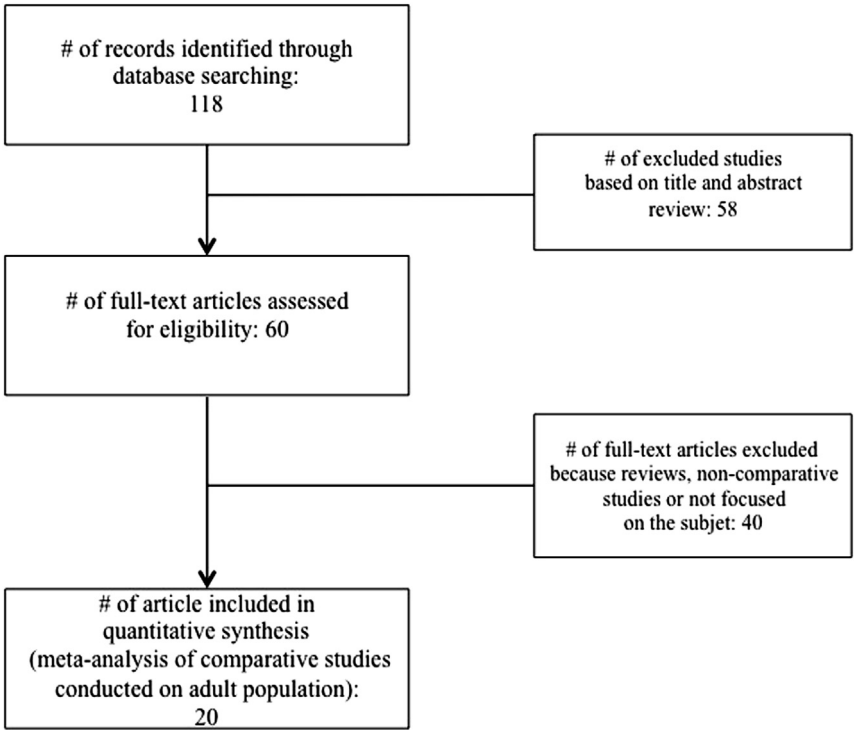

Fig. 1 – Systematic search and selection of articles for meta-analysis.

rate of transient RLN palsy per nerve at low risk was 0.017 *versus* 0.029 in the IONM and VA groups, respectively. This difference was not statistically significant (OR = 0.581, 95% CI = 0.284–1.190; no heterogeneity was found for Q = 0.254, P = 0.613; Table 4). The rate of permanent RLN palsy per nerve at low risk was 0.006 *versus* 0.007 in the IONM and VA groups, respectively, and this difference was also not statistically significant (OR = 0.822, 95% CI = 0.220–3.074; no heterogeneity was found for Q = 0.222, P = 0.637; Fig. 8, Table 4).

3.2.3. *Overall, transient, and permanent RLN palsy per nerve at high risk*

The meta-analysis of RLN palsy per nerve at high risk was conducted on seven studies that reported the absolute numbers of injuries to nerves considered at high risk [4,7,9,16,21,29,30]. Nerves in thyroidectomies performed for substernal goiter, recurrent goiter, thyroid carcinoma, and Graves' disease were those considered to be at high risk. The rate of overall RLN palsy per nerve at high risk was 0.047 in the IONM group *versus* 0.060 in the VA group (1603 *versus* 1715 total nerves at high risk). This difference was not statistically significant (OR = 0.829, 95% CI = 0.511–1.344; heterogeneity was found for Q = 12.810, P = 0.046; Table 4). The rate of transient RLN palsy per nerve at high risk was 0.034 *versus* 0.044 in the IONM and VA groups, respectively. This difference was not statistically significant (OR = 0.842, 95% CI = 0.477–1.483; heterogeneity was found for Q = 12.942, P = 0.044; Table 4). The rate of permanent RLN palsy per nerve at high risk was 0.012 *versus* 0.017 in the IONM and VA groups, respectively, and this difference was also not statistically significant (OR = 0.763, 95% CI = 0.432–1.347; no heterogeneity was found for Q = 1.119, P = 0.980; Fig. 9, Table 4).

3.2.4. *Assistance in RLN identification before visualization*

This outcome of interest was impossible to meta-analyze, as only one study clearly reported the absolute data about localization before visualization of the RLN. Barczyński *et al.* [7] reported that nerve stimulation allowed localization of 137 out of 1000 RLN nerves before visual nerve exposition, and 92 more bifurcated nerves than RLN visualization alone.

4. Discussion

The use of neuromonitoring in thyroid surgery has gained increasing acceptance among endocrine and head–neck surgeons because of several intraoperative advantages, and it has recently been well standardized [22]. Nevertheless, the results of neuromonitoring during thyroidectomy are still a matter to be debated.

The primary outcome measures of our systematic review with meta-analysis show that there were no statistically significant differences in overall, transient, or permanent RLN palsy per nerve at risk when comparing the results of the IONM group with those of the VA group. Likewise, the rates of overall, transient, and permanent RLN palsy per patient at risk were similar in the IONM and VA groups. Regarding the results of the secondary outcomes, the meta-analysis of RLN palsy per nerve at low and high risk showed that the rates of overall, transient, and permanent palsy were comparable in both groups, without statistically significant differences. The length of operative time of total thyroidectomy was also similar in both groups. The outcome of interest regarding the aid in RLN identification before visualization was impossible

Table 1 – Demographics characteristic of patients and type of operation as reported in the included studies.

Author (y)	Study type	No. of patients		Age (y)		Sex (F/M)		TT/other interventions	
		IONM	VA	IONM	VA	IONM	VA	IONM	VA
Calò *et al.* 2013 [13]	RCS	751	942	–	–	563/188	785/157	742/9	902/40
Alesina *et al.* 2012 [16]	RCS	89	157	55 ± 12	55 ± 13	78/11	131/26	35/54	31/126
Gremillion *et al.* 2012 [18]	RCS	31	88	–	–	–	–	10/21	33/55
Stevens *et al.* 2012 [1]	PCS	39	52	48.6 ± 12.1	48.1 ± 13.6	26/13	28/24	23/16	29/23
Barczynski *et al.* 2011 [29]	PCS	151	151	43.9 ± 18.1	44.9 ± 15.7	137/14	135/16	151/0	151/0
Duclos *et al.* 2011 [17]	PCS	475	211	53.3	54.0	361/114	171/40	403/72	171/40
Frattini *et al.* 2010 [30]	RCS	76	76	41	39.8	40/36	45/31	76/0	76/0
Sari *et al.* 2010 [11]	RCT	123	114	47.2 ± 14	48.3 ± 12	104/19	91/23	23/100	26/88
Atallah *et al.* 2009 [21]	RCS	112	149	–	–	–	–	–	–
Barczynski *et al.* 2009 [7]	RCT	500	500	51.9 ± 14.7	51.3 ± 14.4	457/43	455/45	371/129	378/122
Dionigi *et al.* 2009 [31]	RCT	36	36	41	39.8	32/4	30/6	19/17	21/15
Agha *et al.* 2008 [32]	RCS	18	41	–	–	–	–	–	–
Netto *et al.* 2007 [33]	PCS	104	100	43	65/39	96/8	88/12	65/39	58/42
Shindo *et al.* 2007 [20]	RCS	427	257	–	–	–	–	244/183	115/142
Terris *et al.* 2007 [34]	PCS	73	64	–	–	–	–	19/54	20/44
Chan *et al.* 2006 [9]	PCS	316	323	–	–	–	–	183/133	171/152
Witt *et al.* 2005 [35]	RCS	54	83	–	–	–	–	–	–
Dralle *et al.* 2004 [4]	PCS*	–	–	–	–	–	–	–	–
Robertson *et al.* 2004 [12]	RCS	82	83	–	–	–	–	–	–
Yarbrough *et al.* 2004 [36]	RCS	52	59	51.1	50.4	33/19	37/22	–	–

PCS = prospective comparative study; RCS = retrospective comparative study; TT = total thyroidectomy.
*Overall 16,517 patients not identified per group, but specified per nerve at risk (17,832 *versus* 5517 nerves at risk in IONM and VA group, respectively).

to meta-analyze, as only one study clearly reported this outcome [7].

Thus, with regard to the aim of the present research, the analysis of our results can be interpreted as indicating that there is no real benefit of IONM over VA in reducing the rate of RLN palsy.

The total number of nerves at risk was 35,513, with 24,038 nerves in the IONM group and 11,475 nerves in the VA group.

Table 2 – Methods for IONM as reported in the included studies.

Author (y)	Operative time (min)*		Device
	IONM	VA	
Calò *et al.* 2013 [13]	–	–	NIM Response 2.0/3.0 Monitor (Medtronic Xomed, Jacksonville, FL)
Alesina *et al.* 2012 [16]	99 ± 43	80 ± 27	Neurosign (InoMed, Teningen Germany); since 2010 NIM 3.0 (Medtronic Xomed)
Gremillion *et al.* 2012 [18]	99.8 ± 40.0	102.4 ± 27.3	Prass stimulator probe (Medtronic Xomed); EMG Contact Endotracheal Tube (IOM Products, INC, Ventura, CA)
Stevens *et al.* 2012 [1]	180	132.5	NIM (Medtronic Xomed)
Barczynski *et al.* 2011 [29]	–	–	Neurosign 100 Unit (Inomed) and NIM 2.0 Unit (Medtronic Xomed)
Duclos *et al.* 2011 [17]	–	–	NIM Response System (Medtronic Xomed)
Frattini *et al.* 2010 [30]	–	–	NIM Response 2.0 System, (Medtronic Xomed)
Sari *et al.* 2010 [11]	65.4 ± 31	79.1 ± 30	Endotracheal-Based Monitoring System (NIM)
Atallah *et al.* 2009 [21]	–	–	NIM Response 2.0 (Medtronic Xomed)
Barczynski *et al.* 2009 [7]	104.8 ± 26.7	95.7 ± 24.7	Neurosign 100 system (Ionmed,)
Dionigi *et al.* 2009 [31]	97.6	95.0	NIM Response 2.0 system (Medtronic Xomed)
Agha *et al.* 2008 [32]	–	–	IONM not specified
Netto *et al.* 2007 [33]	162.5	–	NIM-2 (Medtronic Xomed)
Shindo *et al.* 2007 [20]	–	–	NIM-2 (Medtronic Xomed)
Terris *et al.* 2007 [34]	–	–	NIM-2
Chan *et al.* 2006 [9]	119 ± 51	116 ± 37	Neurosign 100 machine (Magstim Clarify Company, Withland, UK)
Witt *et al.* 2005 [35]	–	–	NIM (MedTronic, Minneapolis, MN)
Dralle *et al.* 2004 [4]	–	–	Neurosign 100 system (Ionmed)
Robertson *et al.* 2004 [12]	–	–	NIM EMG endoctracheal tube and NIM-2 (Medtronic Xomed)
Yarbrough *et al.* 2004 [36]	–	–	IONM not specified

NIM = nerve integrity monitor.
*Operative times are referred to total thyroidectomy.

Table 3 – Postoperative morbidity in terms of overall, transient and permanent RLN palsy per patient and per nerve at risk.

Author (y)	No. of patients		Nerves at risk		Overall		Total transient		Total permanent	
	IONM	VA	IONM	VA	IONM	VA	IONM	VA	IONM	VA
Calò *et al.* 2013 [13]	751	942	1493	1844	20	28	14	21	6	7
Alesina *et al.* 2012 [16]	89	157	128	161	8	4	8	4	0	0
Gremillion *et al.* 2012 [18]	31	88	41	121	2	4	2	3	0	1
Stevens *et al.* 2012 [1]	39	52	62	81	5	5	4	3	1	2
Barczynski *et al.* 2011 [29]	151	151	302	302	5	10	3	8	2	2
Duclos *et al.* 2011 [17]	475	211	878	382	36	10	–	–	–	-
Frattini *et al.* 2010 [30]	76	76	152	152	3	7	2	5	1	2
Sari *et al.* 2010 [11]	123	114	210	199	3	3	3	3	0	0
Atallah *et al.* 2009 [21]	112	149	181	240	16	22	9	13	7	9
Barczynski *et al.* 2009 [7]	500	500	1000	1000	27	50	19	38	8	12
Dionigi *et al.* 2009 [31]	36	36	55	57	1	3	1	3	0	0
Agha *et al.* 2008 [32]	18	41	–	–	1	4	–	–	–	-
Netto *et al.* 2007 [33]	104	100	169	158	12	12	6	7	6	5
Shindo *et al.* 2007 [20]	427	257	671	372	25	17	16	9	2	1
Terris *et al.* 2007 [34]	73	64	92	84	4	5	4	5	0	0
Chan *et al.* 2006 [9]	316	323	501	499	21	26	17	20	4	6
Witt *et al.* 2005 [35]	54	83	83	107	6	4	4	3	2	1
Dralle *et al.* 2004* [4]	–	–	17,832	5517	626	193	483	144	143	49
Robertson *et al.* 2004 [12]	82	83	116	120	5	8	4	5	1	3
Yarbrough *et al.* 2004 [36]	52	59	72	79	11	11	9	8	2	3
Total per patient at risk	3509	3486	–	–	211 (6.0%)	233 (6.7%)	125 (3.5%)	158 (4.5%)	42 (1.2%)	54 (1.5%)
Total per nerve at risk	–	–	24,038	11,475	837 (3.5%)	426 (3.7%)	608 (2.5%)	302 (2.6%)	185 (0.8%)	103 (0.9%)

*Overall 16,517 patients not divided per group, but identified per absolute numbers of nerves at risk.

The rate of overall RLN palsy per nerve at risk was 3.47% in the IONM group and 3.67% in the VA group. The rate of transient RLN palsy per nerve at risk was 2.62% *versus* 2.72% in the IONM and VA groups, respectively. The rate of permanent RLN palsy per nerve at risk was 0.79% *versus* 0.92% in the IONM and VA groups, respectively. Overall, the prevalence of RLN damage tended to be lower in the IONM group, but no statistically significant differences were found.

In connection with these typical rates of definitive nerve palsy, it has been estimated that in the setting of a prospective, randomized trial, the calculated sample size needed to prove that rates of paralysis are lower with the use of IONM is around 9000 nerves at risk [24]. Other authors reported that at least 39,907 nerves at risk per arm would be necessary for thyroid cancer only to reach a statistical power with significant difference in RLN palsy rate [4]. The high number of patients required shows the difficulty of undertaking such a trial. To date, only three controlled trials comparing the two techniques have been published [7,11,31]. These trials, which include hundreds of patients, might not be adequate for performing a meta-analysis with the required statistical power, because of an inherent type II error [24]. On the other hand, the use of a pooled analysis including a large number of observational studies involving thousands of patients, with

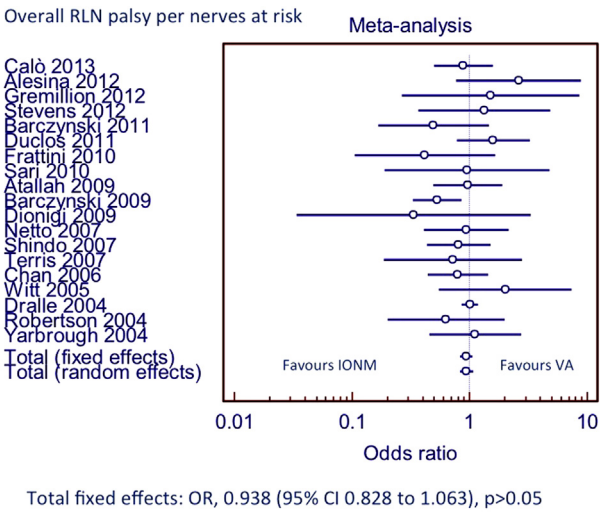

Fig. 2 – Meta-analysis of overall RLN palsy per nerve at risk. (Color version of figure is available online.)

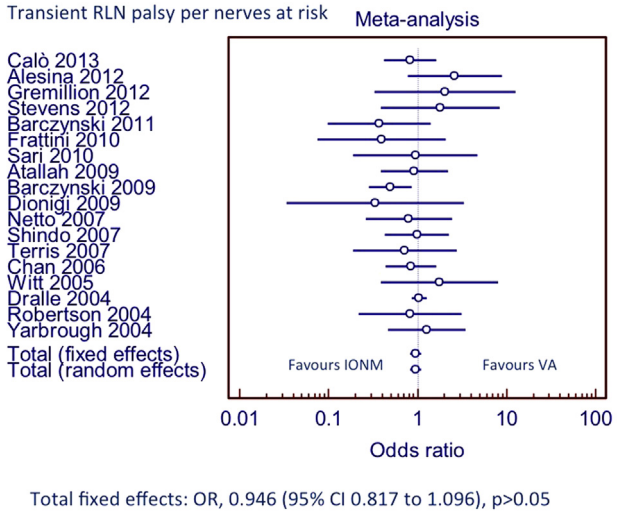

Fig. 3 – Meta-analysis of transient RLN palsy per nerve at risk. (Color version of figure is available online.)

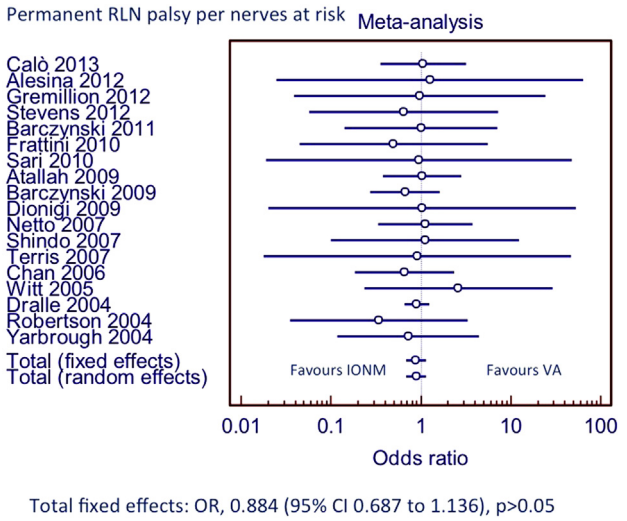

Fig. 4 – Meta-analysis of permanent RLN palsy per nerve at risk. (Color version of figure is available online.)

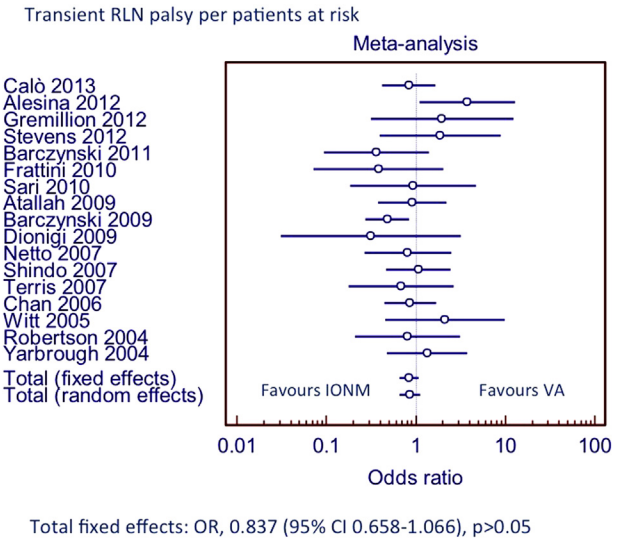

Fig. 6 – Meta-analysis of transient RLN palsy per patient at risk. (Color version of figure is available online.)

>35,000 nerves at risk, appears justified in the absence of adequately powered RCTs [26]. When calculating the primary outcomes for our research, there was no heterogeneity across the included studies, which showed no true differences in the study effect. Nevertheless, meta-analyses based on observational design studies are prone to bias such as selection, allocation, performance, and interventional biases, causing low-level evidence [37].

To the best of our knowledge, this is the third meta-analysis to match well the results of IONM *versus* VA of RLN in thyroid surgery. The meta-analysis by Higgins *et al.* [23] included one RCT, eight comparative observational studies, and 34 noncomparative case series. The analysis included comparative studies together with noncomparative studies, which were pooled in a whole subgroup of patients. This methodology caused heterogeneity across studies, allowing only the use of the random effects model to estimate all end points. On the other hand, our meta-analysis included only comparative studies showing homogeneity with regard to the assessment of the outcomes of interest using the fixed effects model. This means that if all included studies were infinitely large, they would yield identical estimates of the effect.

The meta-analysis by Sanabria *et al.* [24] included six RCTs. Three of those studies focused on the outcome of monitoring the external branch of the superior laryngeal nerve [38–40], and three focused on the results of IONM *versus* VA of RLN. Thus, the total number of patients included in this pooled analysis might not be adequate to reach a statistically significant difference between groups when evaluating the outcomes of RLN palsy.

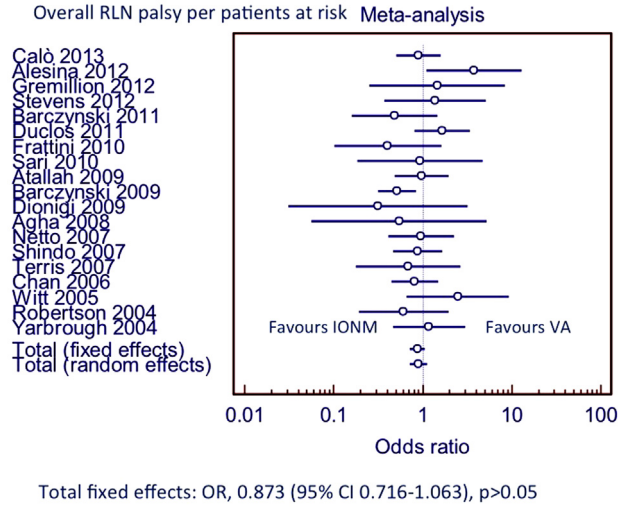

Fig. 5 – Meta-analysis of overall RLN palsy per patient at risk. (Color version of figure is available online.)

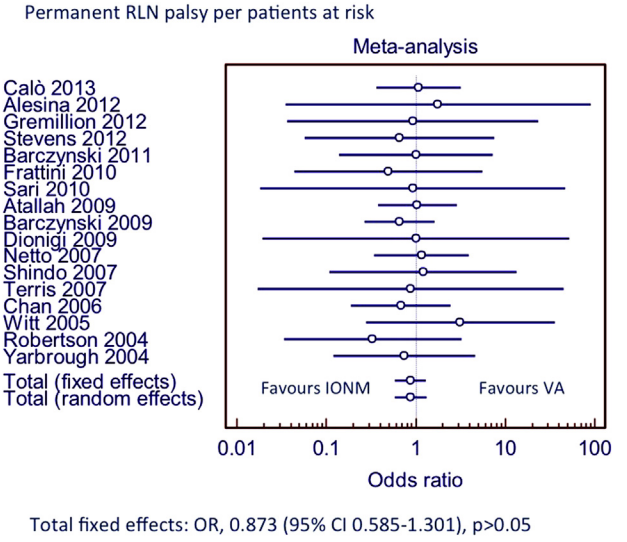

Fig. 7 – Meta-analysis of permanent RLN palsy per patient at risk. (Color version of figure is available online.)

Table 4 – Overall transient and permanent RLN palsy in low and high risk nerves.

Author (y)	Nerves at low risk		Low risk overall		Low risk transient		Low risk permanent		Nerves at high risk		High risk overall		High risk transient		High risk permanent	
	IONM	VA	IONM	VA	IONM	VA	IONM	VA	IONM	VA	IONM	VA	IONM	VA	IONM	VA
Alesina *et al.* 2012 [16]	–	–	–	–	–	–	–	–	89	157	8	4	8	4	0	0
Barczynski *et al.* 2011 [29]	–	–	–	–	–	–	–	–	302	302	5	10	3	8	2	2
Frattini *et al.* 2010 [30]	–	–	–	–	–	–	–	–	152	152	3	7	2	5	1	2
Atallah *et al.* 2009 [21]	–	–	–	–	–	–	–	–	181	240	16	22	9	13	7	9
Barczynski *et al.* 2009 [7]	494	508	12	17	9	14	3	3	506	492	15	33	10	24	5	9
Chan *et al.* 2006 [9]	200	206	4	9	3	7	1	2	301	293	17	17	14	13	3	4
Yarbrough *et al.* 2004 [36]	–	–	–	–	–	–	–	–	72	79	11	11	9	8	2	3
Total per nerve at risk	694	714	16 (2.3%)	26 (3.6%)	12 (1.7%)	21 (2.9%)	4 (0.6%)	5 (0.7%)	1603	1715	75 (4.7%)	104 (6.0%)	55(3.4%)	75(4.4%)	20(1.2%)	29(1.7%)

We included data from those studies that reported the absolute numbers of RLN palsy of nerves at low and high risk.

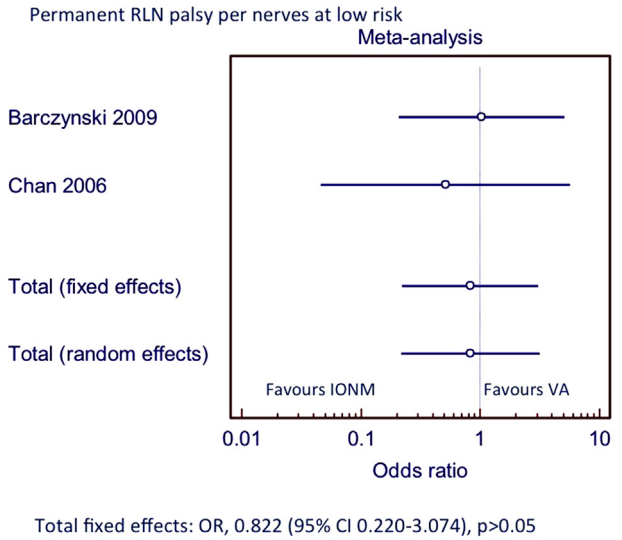

Fig. 8 – Meta-analysis of permanent RLN palsy per nerve at low risk. (Color version of figure is available online.)

Currently, the use of neuromonitoring in thyroid surgery is affected by some limitations, and thus, there is no consensus of its true effectiveness. Regarding the occurrence of vocal cord palsy, the outcome is excellent for patients with an intact monitoring signal at the end of the operation, which is consistent with the high negative predictive value of the procedure, reported to be as high as 97% or even 99% [4,7].

The outcome on vocal cord status is extremely unpredictable when there is a loss of signal at the end of a thyroidectomy because of the low positive predictive value (PPV) of the procedure, which is around 33%–37.8% [4,7]. This means that two-thirds of nerves with a missing monitoring signal can expect normal vocal cord function after surgery [7,10]. The relatively low sensitivity and PPV is one of the major concerns in the use of neuromonitoring. Strict criteria

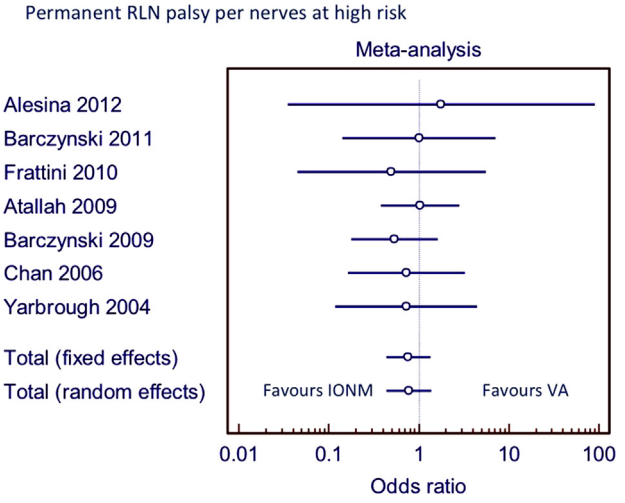

Fig. 9 – Meta-analysis of permanent RLN palsy per nerve at high risk. (Color version of figure is available online.)

of standardization, as described elsewhere [22], can reduce technical pitfalls, thereby improving the PPV of neuromonitoring [4,10].

One of the recommendations in the use of neuromonitoring is to avoid contralateral lobe resection after loss of signal in the first lobe [7,10]. The reconsideration of surgical strategy after a missing signal in one site must be evaluated, mainly for redo surgery in patients at major risk of bilateral RLN palsy [41]. Following this recommendation, however, two-thirds of patients might require unnecessary two-stage thyroidectomy [7].

Another highlighted limit of conventional intermittent monitoring is that RLN palsy is usually identified after it has occurred [42]. Real-time continuous intraoperative vagus monitoring can detect an impending RLN injury with modification of the intraoperative strategy, thus avoiding nerve damage [42,43]. However, other authors have reported that the use of continuous neuromonitoring during thyroidectomy does not reduce the rates of RLN palsy compared with neurostimulation alone [44].

The results of this review and meta-analysis show no significant benefit of IONM over VA in reducing the rate of RLN palsy. The rates of permanent RLN palsy per nerve at risk were 0.79% *versus* 0.92% in the IONM and VA groups, respectively. Experienced thyroid surgeons who achieve a RLN morbidity rate <1% will have a low margin of improvement by using neuromonitoring [7,24]. However, a detailed subgroup analysis conducted by Dralle *et al.* [4] showed a significant reduction in the incidence of permanent RLN palsy in low-volume surgeons who adopted IONM during thyroidectomy. In addition, the assistance in nerve identification before visualization could result in a significant decrease in the prevalence of transient RLN palsy [7]. With regard to the previous considerations, it appears that additional research is necessary to understand definitively the different clinical, scientific, and neurophysiological aspects of intraoperative monitoring of the RLN during thyroidectomy [45].

5. Conclusions

It was expected that thyroidectomy with IONM of the RLN would have a positive impact on nerve palsy prevention and nerve identification in some clinical circumstances. However, the results of our study could be interpreted as indicating that there are no real observed benefits of IONM over VA in reducing the rate of RLN palsy. The inherent biases of the current research suggest that the results should be approached with caution. Further studies, including high-quality multicenter prospective, randomized trials based on strict criteria of standardization and subsequent clustered meta-analysis are required to better assess the effectiveness of the IONM procedure in thyroid surgery.

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The authors declare no conflict of interest.

Author contributions: Pisanu A: Conception and design, acquisition and interpretation of data, drafting the article, revising for important intellectual content and approval of the final version.

Porceddu G: Acquisition of data and analysis, revising for intellectual content, approval of the final version.

Podda M: Analysis and interpretation of data, revising for intellectual content, approval of the final version.

Cois A: Analysis and interpretation of data, revising for intellectual content, approval of the final version.

Uccheddu A: Conception and design, interpretation of data, revising for important intellectual content, and approval of the final version.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jss.2013.12.022.

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