Clinical Review

"The final countdown": Is intraoperative, intermittent neuromonitoring really useful in preventing permanent nerve palsy? Evidence from a meta-analysis

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Background. *The aim of our research was to explore the specific role of intermittent intraoperative neuromonitoring (IONM) versus visualization alone in preventing permanent nerve palsy in thyroid surgery.*
Methods. *A systematic review was conducted by searching electronic databases using specific keywords and completed by hand search. The article selection process was carried out by 2 independent investigators using well-defined inclusion and exclusion criteria. Articles evaluating the role of IONM versus visualization alone in preventing recurrent laryngeal nerve palsy were evaluated for inclusion. The relative risk with a confidence interval of 95% was estimated for nonrandomized studies, and risk difference was estimated for randomized control studies. Subgroup meta-analyses were carried out stratifying the studies on the basis of the design and the definition of permanent injury. The heterogeneity among the studies was evaluated with Higgins' Index.*
Results. *A total of 14 articles were included; of these, 10 were nonrandomized studies and 4 were randomized control studies. With regard to the meta-analyses, including nonrandomized studies that defined as permanent an injury persisting for 6 months or 12 months after thyroid surgery, the overall relative risks were, respectively, 0.79 (confidence interval 95%, 0.60–1.05) and 0.75 (confidence interval 95%, 0.43–1.30). As for the meta-analysis including randomized control studies, the risk difference was 0.00 (confidence interval 95%, −0.01 to 0.00). No heterogeneity was found in any of the analyses conducted (Higgins' Index = 0%).*
Conclusion. *Our results show that the use of IONM does not prevent permanent nerve palsy; no significant benefit of IONM over visualization alone in reducing the rate of recurrent laryngeal nerve injuries could be proven. In conclusion, IONM should not be considered the standard care in preventing recurrent laryngeal nerve palsy. (Surgery 2016;160:1693-706.)*

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Recurrent laryngeal nerve (rln) palsy (RLNP) is one of the most feared complications in thyroid surgery. The injury of laryngeal nerves is a cause of disability and of reduced quality of life and occupational function, and it is the most common reason for malpractice litigation in thyroid surgery.[1] Overall, the reported rates of recurrent nerve injury range from 0–6%, but about 50–88%

of all RLNPs are transient.[2] However, many series report a lower incidence of RLNP by 1–2%, with an incidence of permanent palsy in <1% of the cases performed by experienced surgeons.[3]

The risk of lesion of the RLN exists in all neck dissection; the individual mechanism of injury includes stretch, traction, compression or crush, and thermal, electrical, and severing injuries.[4,5] Moreover, some conditions pose a higher risk of nerve injury, such as lack of identification of RLN during surgery, bilateral surgery, surgery for malignant diseases, lymph node dissection, Graves disease and thyroiditis, previous neck surgery, substernal goiter, longer operative times or greater blood loss, and reoperation for neck haematoma.[6] Anatomic integrity, however, does not imply functional integrity, and the inability to intraoperatively visualize the movement of vocal cords implies uncertainty about the postoperative functional outcome.[7]

For these reasons, several methods for RLN monitoring during neck dissection have been explored in recent years. Neuromonitoring has only been introduced into clinical practice over the last 2 decades, but the earliest devices began to be employed in the 1970s with the purpose of reducing this complication by helping the surgeon to identify the laryngeal nerves.[8] Continuous intraoperative neuromonitoring is currently one of the most important intraoperative neural monitoring trends in thyroid surgery, consisting of real-time monitoring of the vagus nerve in order to prevent recurrent laryngeal nerve damage.[9,10]

Intermittent intraoperative neuromonitoring (IONM), however, is still a commonly used method. Several methods of IOMN have been evaluated.[6,11-17] At present, the most widespread and preferred method for IONM is a technique employing endotracheal tube surface electrodes placed in contact with the mucosa of the vocal cord. Once the RLN is identified, stimulation is delivered by applying a bipolar probe, which conveys electric current ranging from 0.5–1.5 mA at a frequency of 30 Hz. The identification of a healthy RLN is confirmed by the visual display of the electromyography waveform and by a series of acoustic signals generated by the device.[3,18]

In the literature, the role of IONM during thyroid surgery is still under debate, as no consensus exists concerning the prevention of RLN injury.[5] Over the last years, many authors have concluded, on the grounds of a meta-analysis,[19-22] that there are no real differences in complication rates between patients who underwent thyroidectomy with IONM and those who did not. Despite this evidence, however, the intraoperative nerve monitoring of the RLN continues to be widely used in thyroid surgery.

Furthermore, no meta-analyses focusing solely on IONM exist in the current literature: All of the available analyses evaluate both intermittent and continuous nerve monitoring. In light of these considerations, the aim of our research is to explore, through accurate methodology, the specific role of IONM versus visualization alone in preventing permanent RLNPs in thyroid surgery.

MATERIALS AND METHODS

This study was conducted throughout a systematic review using the Population Intervention Comparison and Outcome (PICO) model[23] and following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[24] The PICO framework for this study was (P) patients undergoing thyroid surgery, (I) patients operated using IONM of RLN, (C) patients operated without IONM of RLN, and (O) permanent injuries of the RLN.

Search strategy and articles selection. A systematic search was carried out by querying the electronic databases PubMed, Scopus, and Cochrane Central Register of Controlled Trials. The search strings used for the Web search were built using the terms "intraoperative neurophysiological monitoring," "neuromonitoring," "nerve monitoring system," "thyroidectomy," "thyroid surgery," "recurrent laryngeal nerve," "nerve palsy," "vocal cord paralysis," their synonyms, and the Boolean "OR" or "AND." The literature search was conducted until August 2014 and was completed by hand searching relevant articles from reference lists.

Two independent investigators (G.C. and A.A.) screened the article titles and abstracts to identify potentially relevant publications. The full texts of the articles considered to meet the criteria for inclusion were obtained and evaluated in duplicate. All discrepancies between the 2 investigators were resolved by consensus. The inclusion criteria for this review were articles published in English that compared postoperative permanent injuries of RLN in patients undergoing thyroid operations with IONM versus without IONM.

Articles were excluded if they did not meet the inclusion criteria or if they met ≥1 of the following exclusion criteria: evaluating a continuous neuromonitoring system, not reporting the number of permanent injuries as nerve at risk (NAR), not reporting the preoperative evaluation of vocal cord function, not excluding patients with preoperative vocal cord injuries, review articles, descriptive articles, animal studies, case series, case reports, and other noncontrolled studies.

Data extraction and quality assessment. The following data were extracted from the studies included in the review: first author, year and country of publication, study design, total number of patients, total number of NAR, the number of NAR in operative procedures using IONM or without using IONM, device used, preoperative evaluation, outcome measurement technique, number of RLN permanently injured as NAR, and main results of the study.

The articles were classified on the basis of study design as randomized controlled trials (RCTs) and nonrandomized studies (NRSs) that comprise both the prospective NRSs and prospective or retrospective cohort studies. Quality assessment of the included studies was performed in duplicate by 2 investigators (G.C. and A.A.) and, according to the Cochrane Collaboration's suggestion, the applied scales were respectively the Cochrane Collaboration's tool for assessing risk of bias in RCTs and the Newcastle-Ottawa Scale for the NRSs.[25] All differences in the judgment were resolved by a third investigator or by consensus.

The Cochrane tools for quality assessment of RCTs consist of 6 domains and a total of 7 items[25]: (1) selection bias (random sequence generation; allocation concealment); (2) performance bias (blinding of participants and personnel); (3) detection bias (blinding of outcome assessment); (4) attrition bias (incomplete outcome data); (5) reporting bias (selective reporting); and (6) other bias (other source of bias). For each of these 6 domains, the tools assign a judgment of "low risk of bias," "high risk of bias," or "unclear risk of bias."

The Newcastle-Ottawa Scale consists of 3 domains and a total of 8 items[26]: (1) selection (representativeness of the exposed cohort; selection of the nonexposed cohort; ascertainment of exposure; demonstration that outcome of interest was not present at start of study); (2) comparability (comparability of cohorts on the basis of the design or analysis); and (3) outcome (assessment of outcome; was follow-up long enough for outcomes to occur; adequacy of follow-up of cohorts).

Statistical analysis. The outcome investigated in this meta-analysis was the risk of permanent injuries of RLN in patients undergoing thyroid surgery with IONM compared to the patients without IONM. The presence of heterogeneity among the studies was investigated by the estimation of the I^2 statistic, which shows the percentage of variability due to heterogeneity rather than the change: An I^2 value of ≥50% indicates a moderate-high level of heterogeneity, as suggested by Higgins et al,[27] and subgroups analyses could be performed.

Several factors were considered to be a potential source of heterogeneity, such as the presence or absence of randomization and the different definitions of permanent palsy. To better control the heterogeneity, the studies included in the quantitative analysis were divided into 2 groups on the basis of the study design: one meta-analysis for the RCTs and one for the NRSs.

As for the meta-analysis of the NRSs, the studies included in this group were divided into 2 further subgroups on the basis of the different definitions of permanent RLN injuries: one subgroup comprised the studies in which the authors defined as permanent an injury persisting after 6 months, and the other comprised the studies in which the authors defined as permanent an injury persisting after 12 months. Articles with different definitions, or those in which the authors did not specify the meaning of a permanent injury, were excluded.

The relative risk (RR) with 95% confidence interval (CI) was used to quantify this association. For each included study, the RR was extracted or, where not available, was calculated using presented data. The results were reported on a forest plot graph based on a fixed-effects model (because of the lack of heterogeneity), where the RRs and the corresponding 95% CI for each study were listed.

An RR equal to 1 indicates that there is no difference in the risk of RLN permanent injuries using IONM or not in patients undergoing a thyroid operation; an RR >1 suggests that the use of IONM increases the risk of permanent RLN injuries compared to not using this technique, while an RR <1 suggests that the use of IONM reduces the risk of permanent RLN injuries compared to not using it. On the basis of the absence of the value 1 within the 95% CI, the RR was considered statistically significant.

As for the meta-analysis of the RCTs, the stratification of the studies in subgroups according to the different definition of permanent injuries was not possible due to the scarcity of articles. Since the number of events in both the IONM and non-IONM groups was equal to zero in 3 of the 4 RCTs included, and according to the indications of the Cochrane Collaboration,[25] the risk difference (RD) with 95% CI was used as an association measure.

For each included study, the RD was calculated using presented data. The results were reported on

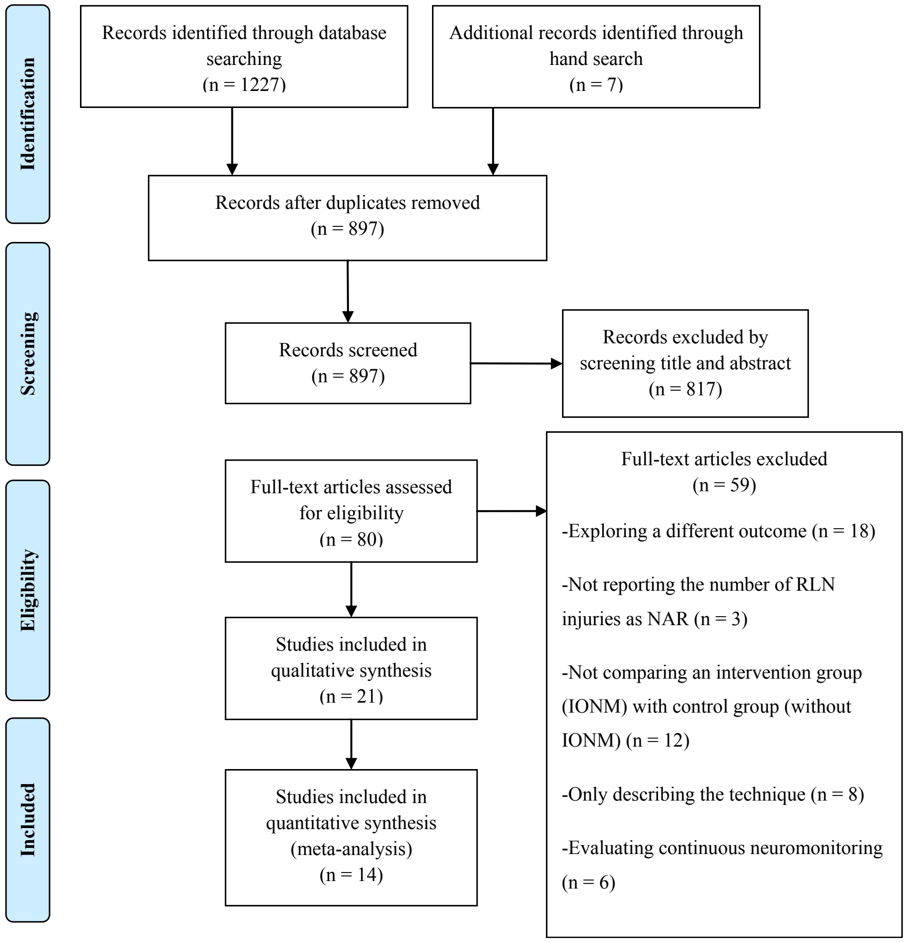

Fig 1. Flowchart of article selection according to PRISMA statement.[24]

a forest plot graph based on a fixed-effects model (I^2 = 0), where the RDs and the corresponding 95% CIs for each study were listed. An RD = 0 indicates the absence of difference in the risk of RLN permanent injuries between the IONM and non-IONM groups; an RD >0 suggests an increased risk of permanent RLN injuries in the IONM group, while an RD <0 suggests a reduction in the risk of permanent RLN injuries using IONM. If the value 0 was not included within the 95% CI, the RD was considered statistically significant. All the meta-analyses were performed using RevMan software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark).

RESULTS

Literature search and study selection. The literature search retrieved a total of 1,227 articles (697 from Scopus, 517 from PubMed, and 6 from Cochrane Central Register of Controlled Trials). As for the results obtained from the Scopus database, the search initially yielded a total of 1,368 citations, but after applying the filters for language (limited to English) and subject area (excluding engineering, chemical engineering, computer science, arts and humanities, agricultural and biological science, materials science, chemistry, dentistry, physics and astronomy, social science, immunology and microbiology, mathematics, environmental science, and veterinary), the final number of records was 697.

Once the duplicates were removed, 897 unique records were finally reviewed. With the application of the inclusion and exclusion criteria to the titles and abstracts, 817 articles were excluded and 80 potentially relevant full-text articles were obtained and reviewed. After reading the full-text articles, 20 of them were included in the review and, of these, 14 articles were included in the quantitative synthesis: 4 RCTs[28-31] and 10 NRSs.[7,9,18,32-38] A flowchart describing the article selection process is shown in Fig 1.

Table I. Main characteristics of the selected studies

Author year	*Title*	*Preoperative diagnosis*	*Inclusion criteria*	*Exclusion criteria*	*Allocation method*	*Device used*	*Outcome measurement*	*Main results*
Alesina 2012[32]	Intraoperative neuromonitoring does not reduce the incidence of recurrent laryngeal nerve palsy in thyroid reoperations: results of a retrospective comparative analysis	Recurrent goiter Hyperthyroidism Recurrent thyroid cancer	Thyroid reoperations	Interventions on not previously operated sites Completion of thyroidectomy	Device availability Personal preference	Neurosign (InoMed, Teningen Germany) Since 2010 NIM 3.0 (Medtronic Xomed)	Laryngo-scopy	The use of IONM seems not to reduce the incidence of RLN during thyroid reoperations.
Barc-zinsky 2009[28]	Randomized clinical trial of visualization versus neuromonitoring of recurrent laryngeal nerves during thyroidectomy	Bilateral disease	Bilateral neck surgery	Previous thyroid or parathyroid surgery Unilateral pathology eligible for minimally invasive approach Mediastinal goiter Preoperative RLN palsy Pregnancy or lactation <18 y ASA >4* Inability to comply with follow-up	Randomization	Neurosign 100 system (Inomed)	Laryngo-scopy	Nerve monitoring decreased the incidence of transient but not permanent RLN paresis compared with visualization alone, particularly in high-risk patients.
Barc-zinsky 2011[41]	Clinical value of intraoperative neuromonitoring of the recurrent laryngeal nerves in improving outcomes of surgery for well-differentiated thyroid cancer	Thyroid well-differentiated cancer	Total thyroidectomy Patient diagnosed with well-differentiated cancer of thyroid	Recurrence in contralateral lobe after lobectomy	2003–2004 (without IONM) 2005–2009 (with IONM)	Neurosign 100 Unit (Inomed) and NIM 2.0 Unit (Medtronic Xomed)	Laryngoscopy	The use of IONM may improve the outcomes of surgery among patients with WDTC by both increasing the completeness of total thyroidectomy and significantly reducing the prevalence of temporary RLN injury.
Barc-zinsky 2012[29]	Randomized controlled trial of visualization versus neuromonitoring of the external branch of the superior laryngeal nerve during thyroidectomy	Nontoxic nodular goiter Thyroid carcinoma Graves disease Toxic nodular goiter	First time bilateral neck surgery Female sex Small and moderate size goiter	Male gender Previous neck surgery Unilateral surgery Goiter volume >100 mL Preoperatively diagnosed RLN palsy Abnormal preoperative voice assessment GRBAS* scale Pregnancy or lactation <18 y ASA >4 Inability to comply with follow-up protocol	Randomization	NIM 3.0 system (Medtronic Jacksonville, FL)	Laryngoscopy multidimensional evaluation	IONM improved the identification rate of the EBSLN during thyroidectomy, as well as reduced the risk of early phonation changes after thyroidectomy.
Barc-zinsky 2014[33]	Intraoperative nerve monitoring can reduce prevalence of recurrent laryngeal nerve injury in thyroid reoperations: results of a retrospective cohort study	Goiter Recurrent hyperthyroidism Recurrent thyroid cancer Completion thyroidectomy	Reoperations	Recurrence in contralateral lobe after lobectomy	NS	Neurosign 100 Unit (Inomed) and NIM 2.0 and NIM 3.0 (Medtronic, Jacksonville)	Laryngoscopy	IONM decreased the incidence of transient RLN paresis in repeat operations and the prevalence of permanent RLN injuries tended to be lower.

(*continued*)

Table I. (*continued*)

Author year	*Title*	*Preoperative diagnosis*	*Inclusion criteria*	*Exclusion criteria*	*Allocation method*	*Device used*	*Outcome measurement*	*Main results*
Brauck-hoff 2002[39]	First experiences in intraoperative neurostimulation of the recurrent laryngeal nerve during thyroid surgery of children and adolescents	Nodular goiter Thyroid carcinoma Graves disease	Children and adolescents	Preoperative palsy Resection of RLN	1995–1997 (without IONM) from 1998 (with IONM)	NS	Laryngoscopy	The intraoperative neuromonitoring may reduce nerve damage.
Calò 2013[42]	Intraoperative recurrent laryngeal nerve monitoring in thyroid surgery: is it really useful?	MNG Differentiated cancer Hashimoto Graves disease Medullary carcinoma	Thyroidectomy	NS	Surgical team availability	NIM Response 2.0/3.0 Monitor (Medtronic Xomed, Jacksonville, FL)	Laryngoscopy	Neuromonitoring is useful to identify the RLN and it can be a useful adjunctive technique for reassuring surgeons of the functional integrity of the nerve but it does not decrease the incidence of injuries compared with visualization alone.
Calò 2014[34]	Identification alone versus intraoperative neuromonitoring of the recurrent laryngeal nerve during thyroid surgery: experience of 2034 consecutive patients	MNG Differentiated cancer Hashimoto Graves disease Medullary carcinoma	Thyroidectomy	Patients in which neuromonitor did not function properly	Surgical team availability	NIM Response 2.0/3.0 Monitor (Medtronic Xomed)	Laryngoscopy	Neuromonitoring helps to identify the nerve, but it did not decrease nerve injuries.
Calò 2014[43]	Role of intraoperative neuromonitoring of recurrent laryngeal nerves in the outcomes of surgery for thyroid cancer	Thyroid cancer	Thyroidectomy in thyroid cancer	Patients in which neuromonitor did not function properly	Surgical team availability	NIM Response 2.0/3.0 Monitor (Medtronic Xomed)	Evaluation of vocal cord mobility	Intraoperative neuromonitoring did not reduce the rate of transient or permanent RLN injuries; IONM has been confirmed to present a high accuracy, sensitivity, specificity, positive and negative predictive value in excluding postoperative RLN palsy; IONM can help to identify the nerve in patients with thyroid cancer.
Chan 2006[18]	The role of intraoperative neuromonitoring of recurrent laryngeal nerve during thyroidectomy: a comparative study on 1,000 nerves at risk	Nodular goiter Graves disease Thyroid cancer Follicular adenoma Thyroiditis	Thyroid surgery	Tumor involvement of RLN	Device availability Team preference	Neurosign 100 machine (Magstim Clarify Company, Whitland, UK)	Laryngoscopy	Neuromonitoring of the RLN during thyroid surgery could not be demonstrated to reduce RLN injury significantly. For selected high-risk patients, the IONM may be associated with an improved outcome.

(*continued*)

Table I. (*continued*)

Author year	*Title*	*Preoperative diagnosis*	*Inclusion criteria*	*Exclusion criteria*	*Allocation method*	*Device used*	*Outcome measurement*	*Main results*
De Falco 2014[35]	Double probe intraoperative neuromonitoring with a standardized method in thyroid surgery	Nontoxic MNG Thyroid carcinoma Substernal goiter Graves disease Toxic multinodular goiter Thyroiditis Recurrent goiter	Total thyroidectomy	Previous vocal fold paralysis Thyroidectomy performed during the "learning curve"	October 2009–July 2011 (without IONM) January 2011–October 2011 (with IONM)	Avalanche XT (Dr Langer Medical GmbH–Waldkirch–Germany)	Laryngoscopy	Using IONM improves the ability to identify the RLN and reduction in the incidence rate of transient RLN injuries.
Dionigi 2009[30]	Neuromonitoring and video-assisted thyroidectomy: a prospective, randomized case-control evaluation	Follicular tumor Nodular goiter Hurtle cell neoplasm	Dominant nodule size ≤35 mm Thyroid US estimated volume ≤25 mL "Low risk" papillary thyroid cancer RET gene carriers	Large goiter (thyroid US estimated volume >25 mL) Dominant nodule size >35 mm Advanced cancer Hyperthyroidism Thyroiditis Previous neck irradiation Previous neck surgery Preoperative injury to laryngeal nerves Intraoperative finding of tumor involvement of RLN Lymph node dissections Associated parathyroid disease Concomitant operations outside the neck Local anesthesia Obesity and stocky neck <18 y Inability to provide informed consent	Randomization	NIM-2 (Medtronic Xomed)	Laryngoscopy	Neuromonitoring during VAT is effective in providing identification and function of laryngeal nerves.
Dralle 2004[7]	Risk factors of paralysis and functional outcome after recurrent laryngeal nerve monitoring in thyroid surgery	Benign MNG Immunogenic goiter Benign recurrent goiter Thyroid malignancy Recurrent thyroid malignancy	Reoperated thyroid sites	NS	Device availability Choice of performing surgeon	Neurosign 100 system (Inomed)	Laryngoscopy	RLN monitoring is a promising tool for nerve identification and protection in extended thyroid resection procedures. However, no statistical difference compared with visual nerve identification.
Gremillion 2012[40]	Intraoperative recurrent laryngeal nerve monitoring in thyroid surgery: is it worth the cost?	NS	NS	NS	NS	Prass stimulator probe (Medtronic Xomed); EMG Contact Endotracheal Tube (IOM Products, INC, Ventura, CA)	NS	The use of IONM did not reduce the time of thyroid surgery and did increase the cost.

(*continued*)

Table I. (*continued*)

Author year	Title	Preoperative diagnosis	Inclusion criteria	Exclusion criteria	Allocation method	Device used	Outcome measurement	Main results
Netto 2007[44]	Vocal fold immobility after thyroidectomy with intraoperative recurrent laryngeal nerve monitoring (São Paulo Medical Journal [2007] vol. 125 [3])	Benign diseases Malign diseases	Thyroid surgery	Previous head and neck surgery Preoperative laryngeal abnormalities in videolaryngoscopy	Convenience (patients with insurance plan)	NIM-2 (Medtronic Xomed)	Laryngoscopy	The use of intraoperative nerve monitoring did not decrease the rate of vocal fold immobility.
Sari 2010[31]	Evaluation of recurrent laryngeal nerve monitoring in thyroid surgery	MNG MTG Solitary adenoma Graves disease Toxic adenoma Carcinoma Papillary carcinoma	Patients with benign and malignant goiter disorders underwent thyroidectomy	Preoperative cord dysfunction Reoperative surgery Retrosternal goiter Monitoring dysfunction (likely electrode displacement) Refusal to participate	Randomization	Endotracheal-based monitoring systems (eg, Medtronic NIM, Jacksonville, FL)	Laryngoscopy	It is important to use IONM to decrease the identification time of RLN in the course of thyroidectomy.
Stevens 2012[36]	The impact of recurrent laryngeal neuromonitoring on multidimensional voice outcomes following thyroid surgery	Thyroid cancer Benign inflammatory disease	Thyroid resection	Previous neck operation Documented voice disorders before surgery Lost to follow-up Parathyroidectomy	NS	NIM (Medtronic Xomed)	Multidimensional voice testing	Recurrent laryngeal neuromonitoring did not appear to influence non-RLN injury related VO as measured by a comprehensive multidimensional voice assessment.
Terris 2007[9]	Laryngeal nerve monitoring and minimally invasive thyroid surgery	MNG Papillary carcinoma Follicular adenoma Thyroiditis Hurtle cell neoplasm Benign nodule Adenoma Colloid Graves' disease Follicular carcinoma	Minimal-access thyroidectomy	Local anesthesia	NS	NIM-2 (Medtronic Xomed)	Laryngoscopy	Monitoring of the laryngeal nerves is feasible in minimal-access thyroid surgery and may serve as a meaningful adjunct to the visual identification of nerves.
Thom-usch 2002[37]	Intraoperative neuromonitoring of surgery for benign goiter	Benign goiter	Intraoperative identification of RLN Benign goiter as final diagnosis	Thyroid cancer No intraoperative identification of RLN	Choice of performing surgeon	Neurosign 100 (InoMed, Teningen Germany);	Laryngoscopy	Intraoperative neuromonitoring of the RLN in thyroid surgery is recommended because of significantly lower rates of transient and permanent RLN palsy rates in comparison with conventional RLN identification.
Witt 2005[38]	Recurrent laryngeal nerve electrophysio-logic monitoring in thyroid surgery: The standard of care?	NS	Thyroid surgery	NS	NS	NIM (MedTronic, Minneapolis, MN)	Evaluation of vocal fold mobility	Electrophysiological RLN monitoring was not demonstrated in this paper to reduce the incidence of transient or permanent VFI after thyroid surgery.

*GRBAS scale: overall severity of dysphonia (G), roughness (R), breathiness (B), asthenia (A), and strained (S) quality of the voice.
EBSLN, External branch of superior laryngeal nerve; *MNG*, multinodular goiter; *MTG*, multinodular toxic goiter; *WDTC*, well-differentiated thyroid cancer; *NS*, not specified; *ASA*, American Society of Anesthesiology; *VFI*, vocal fold injuries; *VAT*, video-assisted thyroidectomy; *NIM*, neural integrity monitor; *RLN*, recurrent laryngeal nerve.

Table II. Relevant characteristics of the studies included in quantitative analysis

Author year	Study design	Definition of permanent injuries	Patients (NAR)	No. of NAR		No. of permanent injuries	
				IONM	Non-IONM	IONM	Non-IONM
Alesina 2012[32]	Retrospective NRS	6 months	246 (289)	128	161	0	1
Barczynski 2009[28]	RCT	12 months	1,000 (2,000)	1,000	1,000	8	12
Barczynski 2012[29]	RCT	6 months	201 (402)	200	202	0	0
Barczynski 2014[33]	Retrospective NRS	12 months	854 (1,326)	500	826	7	20
Calò 2014[34]	Retrospective NRS	12 months	2,034	2,068	1,946	8	8
Chan 2006[18]	Prospective NRS	12 months	639 (1,000)	501	499	4	6
De Falco 2014[35]	Retrospective NRS	6 months	600 (1,200)	600	600	4	5
Dionigi 2009[30]	RCT	12 months	(112)	55	57	0	0
Dralle 2004[7]	Prospective NRS	6 months	(23,349)	17,832	5,517	143	48
Sari 2010[31]	RCT	12 months	(409)	210	199	0	0
Stevens 2012[36]	Prospective NRS	6 months	91 (143)	62	81	1	2
Terris 2007[9]	Prospective NRS	6 months	137 (176)	92	84	0	0
Thomusch 2002[37]	Prospective NRS	6 months	4,382 (7,133)	2,483	4,650	9	37
Witt 2005[38]	Retrospective NRS	12 months	136 (190)	83	107	2	1

IONM, Intraoperative neuromonitoring.

Characteristics of the included studies. The main characteristics of the articles selected are shown in Table I. The relevant data extracted from the studies included in quantitative synthesis are shown in Table II. Four studies were conducted in Germany,[7,9,32-39] 4 in the United States,[36-38,40] 4 in Poland,[28,29,33,41] 5 in Italy,[30,34,35,42,43] 1 in China,[18] 1 in Turkey,[31] and 1 in Brazil.[44] The allocation method differed across the studies and comprised randomization for the RCTs, consecutive allocation, surgeon preference, device or team availability, and the convenience on the basis of the availability of a medical insurance for the NRSs. The experience and the number of surgeons involved were also different or, in some studies, not specified. The preoperative diagnosis, the age of the patients involved, and the type of intervention also varied across the studies.

Some studies included a large spectrum of pathology, such as benign or malignant neoplasms, thyroiditis, Graves disease, different types of goiter, and hyperthyroidism.[9,35] Other studies were more restrictive; for example, Alesina et al[32] and Barczinsky et al[33] limited their studies to reoperated patients with recurrent disease on the contralateral site, Brauchoff et al[39] focused on children and adolescent patients, Terris et al[9] included only patients undergoing minimal access thyroidectomy, and Thomusch et al[37] limited their study to patients with benign goiter; 3 studies[38,40,44] did not specify the included diseases. As for the studies included in the meta-analyses, 4 of these were RCTs and 10 were NRSs, 5 of which were conducted retrospectively (retrospective cohort studies) and 5 of which were prospective, nonrandomized studies.

The definition of permanent nerve injuries was variable: It was defined as an injury that persisted after 6 months in 7 studies, 1 of which was an RCT[29] and 6 of which were NRSs,[7,9,32,35-37] and after 12 months in the other 7 studies, 3 of which were RCTs[28,30,31] and 4 of which were NRSs.[18,33,34,38] In the studies by Gremillion et al[40] and Brauchoff et al,[39] the authors did not specify this information (NS), and in the study by Netto et al,[44] a palsy was defined as permanent if persisting 3 months after the operation. The last 3 studies were thus excluded from the meta-analysis. As for the studies by Calò et al,[34,42,43] since the same sample of patients might have been included wholly or partly in each of the 3 studies, we decided to include in quantitative analysis only the study with the larger sample.[34]

Quality assessment. *NRSs.* For the NRSs, on the basis of the Newcastle-Ottawa Scale, the exposed cohort (patients operated using IONM) in all included studies was judged to be well representative of the average in the community, and the nonexposed cohorts (patients operated using IONM) were drawn from the same community of the exposed ones. Furthermore, in all studies, both the exposure (undergoing a thyroid operation with IONM) and the absence of outcome of interest at the start of the studies (RLN permanent palsy by laryngoscopic evaluation of vocal cord function) were ascertained.

For NRSs included in the quantitative synthesis, the cohorts (with IONM and without IONM) were

Table III. Quality assessment of randomized controlled trials using Cochrane Collaboration's tool

References	*Random sequence generation (selection bias)*	*Allocation concealment (selection bias)*	*Blinding of participants and personnel (performance bias)*	*Blinding of outcome assessment (detection bias)*	*Incomplete outcome data (attrition bias)*	*Selective reporting outcome (reporting bias)*	*Other bias*
Barczinsky 2009[28]	+	+	+	+	+	+	+
Barczinsky 2012[29]	+	+	+	+	+	+	+
Dionigi 2009[30]	–	–	?	?	+	+	+
Sari 2010[31]	+	?	?	?	–	+	+

The plus sign indicates a "Low risk of bias," the minus sign indicates a "High risk of bias," and the interrogative point sign indicates an "Unclear risk of bias."

judged to be comparable on the basis of the similar composition in age, sex, distribution of preoperative diagnosis, and the type of intervention, except for the studies by Thomusch et al[37] and Witt et al.[38] For all studies, the assessment of outcome was positively judged because it was obtained from record linkage. The follow-up period in all the studies included in meta-analysis was long enough for the outcome to occur (≥6 months). Only the studies by Terris et al[9] and Witt et al[38] reported patients lost to follow-up, while the other studies reported a complete follow-up for all patients included.

RCTs. The quality assessment for RCTs is shown in Table III. The random sequence generation was judged to have a low risk of bias in 3 of the 4 trials[12,29,31]; only the RCT by Dionigi et al[30] showed a high risk of bias for this item because the randomization method was based on the time of admission. The allocation concealment was found to be at low risk of bias for 2 trials,[12,29] at high risk of bias for the study by Dionigi et al,[30] and at an unclear risk of bias for the study by Sari et al.[31]

Both the blinding of participants and personnel and the blinding of outcome assessment were considered at low risk of bias for 2 RCTs[12,29] but were at an unclear risk of bias for the studies by Dionigi et al[30] and Sari et al,[31] because this information was not well explained in the Methods section. Incomplete outcome data were considered at high risk of bias for Sari et al[31] and at low risk of bias for the other RCTs. All trials showed a low risk of bias for the selective reporting item. No other sources of bias were identified.

Meta-analyses. The articles were stratified into 2 groups according to the study design (Table II): The first meta-analysis was performed for the NRSs and included a total of 10 articles; the second meta-analysis was carried out for the RCTs and included 4 articles.

Meta-analysis for the NRSs. The studies included in this analysis were split into 2 subgroups on the basis of the definition of the permanent RLN injuries, and 2 additional meta-analyses were performed, the first for the studies that defined as permanent an injury that persisted for 6 months and the second for the studies that defined as permanent injuries that persisted for 12 months.

6 MONTHS META-ANALYSIS: This analysis comprised a total of 32,290 NAR; for 21,197 of these, IONM was used during operations, and for 11,093, IONM was not used. As shown in the forest plot (Fig 2), all 6 of the included studies featured their outcome measures on the left of the vertical line (RR <1) thus being in favor of the IONM, but only one proved to be statistically significant.[37] The subtotal RR was estimated to be 0.79, but this result was not statistically significant (CI 95%, 0.60–1.05) and no heterogeneity was found ($I^2 = 0$).

12 MONTHS META-ANALYSIS: In this second stratified meta-analysis, a total number of 6,530 NAR were included; for 3,152 of these, IONM was used during operations, and for 3,378, IONM was not used. As shown in the forest plot (Fig 2), 3 studies had their outcome measures on the left of the vertical line (RR <1), in favor of using IONM, and one on the right (RR >1), in favor of not using the IONM[38]; none of these studies proved statistically significant. The subtotal RR was estimated to be 0.75, thus being in favor of the use of IONM, but this result was not statistically significant (CI 95%, 0.43–1.30), and no heterogeneity was found ($I^2 = 0$). Furthermore, the lower part of Fig 2 features the total RR referred to the nonstratified meta-analysis consisting of a total number of 38,820 NAR, 24,349 in the IONM group and 14,471 in the group without IONM. The total RR was 0.79 (CI 95%, 0.61–1.01) and not statistically significant. No heterogeneity and no subgroup differences were found ($I^2 = 0$).

Meta-analysis for the RCTs. This analysis comprised 4 RCTs and a total number of 2,923 patients; for 1,465 of these, IONM was used during operations, and for 1,458, IONM was not used. As

Study or Subgroup	With Neuromonitoring Events	With Neuromonitoring Total	Without Neuromonitoring Events	Without Neuromonitoring Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Permanent RLN injuries after 6 month						
Alesina 2012	0	128	1	161	1.0%	0.42 [0.02, 10.19]
De Falco 2014	4	600	5	600	3.6%	0.80 [0.22, 2.96]
Dralle 2004	143	17832	48	5517	53.0%	0.92 [0.67, 1.28]
Stevens 2012	1	62	2	81	1.3%	0.65 [0.06, 7.04]
Terris 2007	1	92	1	84	0.8%	0.91 [0.06, 14.37]
Thomusch 2001	9	2483	37	4650	18.6%	0.46 [0.22, 0.94]
Subtotal (95% CI)		**21197**		**11093**	**78.2%**	**0.79 [0.60, 1.05]**
Total events	158		94			
Heterogeneity: $Chi^2 = 3.24$, df = 5 (P = 0.66); $I^2 = 0\%$						
Test for overall effect: Z = 1.59 (P = 0.11)						
Permanent RLN injuries after 12 months						
Barczynski 2014	7	500	20	826	10.9%	0.58 [0.25, 1.36]
Calò a 2014	8	2068	8	1946	6.0%	0.94 [0.35, 2.50]
Chan 2006	4	501	6	499	4.3%	0.66 [0.19, 2.34]
Witt 2004	2	83	1	107	0.6%	2.58 [0.24, 27.95]
Subtotal (95% CI)		**3152**		**3378**	**21.8%**	**0.75 [0.43, 1.30]**
Total events	21		35			
Heterogeneity: $Chi^2 = 1.63$, df = 3 (P = 0.65); $I^2 = 0\%$						
Test for overall effect: Z = 1.02 (P = 0.31)						
Total (95% CI)		**24349**		**14471**	**100.0%**	**0.79 [0.61, 1.01]**
Total events	179		129			
Heterogeneity: $Chi^2 = 4.92$, df = 9 (P = 0.84); $I^2 = 0\%$						
Test for overall effect: Z = 1.88 (P = 0.06)						
Test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.86), $I^2 = 0\%$						

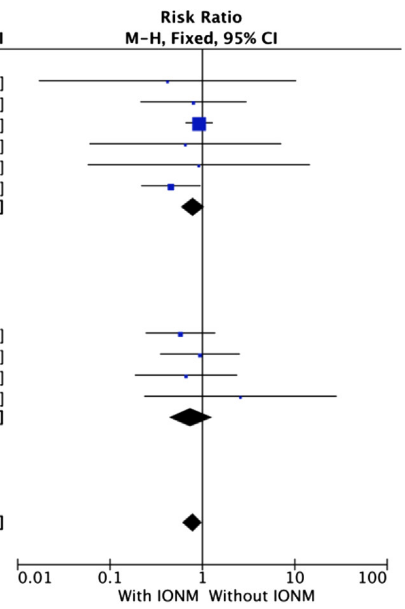

Fig 2. Meta-analysis of the nonrandomized studies comparing the risk of permanent injuries as nerve at risk.

Study	With Neuromonitoring Events	With Neuromonitoring Total	Without Neuromonitoring Events	Without Neuromonitoring Total	Weight	Risk Difference M-H, Fixed, 95% CI
Barczynski 2009	8	1000	12	1000	68.4%	-0.00 [-0.01, 0.00]
Barczynski 2012	0	200	0	202	13.8%	0.00 [-0.01, 0.01]
Dionigi 2009	0	55	0	57	3.8%	0.00 [-0.03, 0.03]
Sari 2010	0	210	0	199	14.0%	0.00 [-0.01, 0.01]
Total (95% CI)		**1465**		**1458**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	8		12			
Heterogeneity: $Chi^2 = 0.73$, df = 3 (P = 0.87); $I^2 = 0\%$						
Test for overall effect: Z = 0.84 (P = 0.40)						

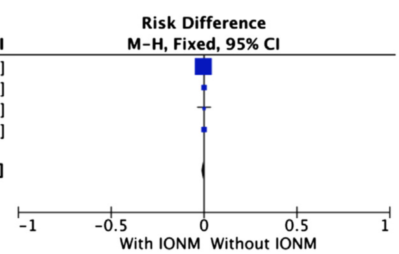

Fig 3. Meta-analysis of the randomized controlled trials study comparing the risk of permanent injuries as nerve at risk.

shown in the forest plot (Fig 3), in 3 of the 4 studies included, no permanent injuries occurred in either the experimental or the control groups. For this reason, the RR could not be estimated, and the results were presented using the RD.[25] The RD proved to be RD = 0 and not statistically significant (CI 95%, −0.01 to 0.00). However, this result confirms the one by the larger study included (Barczinsky et al,[28] weight = 68.4%), which consisted of a total of 2,000 NAR (1,000 in the IONM group and 1,000 in the non-IONM group) and corresponded to an RD = 0.00 with a CI 95% from −0.01 to 0.00. No heterogeneity was found ($I^2 = 0$).

DISCUSSION

The results of this meta-analysis show that the use of IONM brings no significant benefit over visualization alone in reducing the rate of RLN permanent injuries in thyroid operations. These results are confirmed in all meta-analyses performed (meta-analysis of the NRSs with a definition of permanent palsy after 6 months; meta-analysis of NRSs with a definition of permanent palsy after 12 months; meta-analysis of the RCTs), and no heterogeneity was found.

Thus far, 4 reviews with meta-analyses have been performed to compare the results of neuromonitoring of RLN versus visualization alone during thyroidectomy.[19-22] The meta-analysis by Higgins et al[20] is the first one conducted on IONM of the RLN. This study included one RCT, which at the time of the study was the only RCT available, 8 comparative observational studies, and 34 noncomparative case series pooled in a whole subgroup of patients. The results by Higgins et al[20] did not demonstrate a statistically significant difference in preventing RLN injuries between using and not using IONM in thyroidectomy.

The meta-analysis by Pisanu et al[19] concerned the studies comparing IONM of recurrent laryngeal nerves versus visualization alone during thyroidectomy and showed no statistically significant difference in the rate of permanent RLN injuries between using or not using IONM. This study included 3 RCTs, 7 prospective trials, and 10 retrospective, observational studies. Pisanu et al[19] included in their analysis the studies evaluating intermittent and continuous neuromonitoring and, to be more inclusive, also the studies in which the authors did not specify the definition of permanent injuries or did not clarify the preoperative evaluation.

The meta-analysis by Zheng et al[21] included 5 RCTs and 12 comparative trials. The analysis showed a positive effect of IONM in reducing the rate of total and transient RLN palsy, but no significant differences were found in the reduction rates of permanent RLN injuries.

The meta-analysis by Sanabria et al[22] focused only on the RCTs, and both studies focused on the neuromonitoring of the RLN and on the external branch of the superior laryngeal nerve. As for the analysis focused on the RLN palsy, the authors found a nonstatistically significant decrease in the risk of permanent injuries.

On the grounds of these meta-analyses,[19-22] no statistically significant differences were demonstrated in terms of incidence of persistent RLN palsy after using IONM versus visual identification alone. However, in all the meta-analyses, the authors included both the studies that take into consideration intermittent and continuous neuromonitoring. Furthermore, in any of these, a stratification was performed for the different ways of defining permanent paralysis and, in some cases, the authors also included the studies that do not specify this definition.

The Clinical Practice Guidelines existing in the literature[45] suggest that a nerve injury should be considered as permanent if persisting after ≥6 months of follow-up. In a meta-analyses by Pisanu[19] and Zheng[21] the authors decided to also include studies that defined as permanent an injury after 3 months (ie, the study by Gremillion et al[40]) and studies that do not specify the definition of permanent palsy (ie, the article by Pisanu[19] and the study by Brauchoff et al.[39] and the article by Zheng[21]).

Unfortunately, this might be the cause of misclassification; for example, if the permanent paralysis is defined in one study as an injury that persists after 3 months and in another study after 6 months, a patient with a persistent paralysis at 4 months will be considered affected by a permanent injury in the first study and by a transient injury in the second study. For this reason, we decided to include only the articles reporting a definition of permanent palsy as an injury that persists after at least 6 months and to stratify the analysis.

Compared to previous studies, the analyses conducted in the present work are focused on IONM alone, and this criterion represents both a novelty and a strength. By focusing attention on one type of technique, it is possible to more precisely evaluate its advantages and/or disadvantages. The systematic methodology followed in the present study, both in the review process and in the analytic phase, is an important strength. Furthermore, the meta-analyses stratified by study design and by different definitions of permanent paralysis allowed us to better control the heterogeneity ($I^2 = 0\%$).

This study, however, also has some limitations. First, although the search strategy was as rigorous and inclusive as possible, some articles, including studies not in English and unpublished ones, may have been accidentally excluded from the review. Second, with regard to the meta-analysis of the RCTs, estimating an RR was impossible in 3 out of 4 articles, due to the absence of permanent palsy in both the IONM group and the non-IONM group. The standard practice in these cases is to exclude the studies from meta-analysis because they do not provide any indication on the effect of the intervention.[25] To include these trials in meta-analysis and for the sake of completeness in our results, however, we used the RD as the effect measure, as suggested by Cochrane Collaboration and as already done in the study by Sanabria et al.[22] Although this issue might seem to further limit this study, the results confirmed those of the larger trials included and indicate that there is no difference between using or not using IONM.

In conclusion, the results of the present study show that the use of IONM does not prevent permanent nerve palsy; performing IONM brings no significant benefit over visualization alone in reducing the rate of RLN injuries. For these reasons, IONM should not be considered the standard of care. The recent introduction of intraoperative continuous neuromonitoring (continuous intraoperative neuromonitoring) may represent a significant step forward, potentially enabling the surgeon to react before irreversible damage to the RLN occurs. In this context, the use of IONM allowed us to prepare for these changes. Therefore, this research helps to explain the low value of intermittent neuromonitoring in predicting permanent nerve palsy and suggests that future studies should focus on new technologies.

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