

REVIEW ARTICLE

Meta-analysis of recurrent laryngeal nerve injury in thyroid surgery with or without intraoperative nerve monitoring

Meta-analisi del danno dei nervi ricorrenti nella chirurgia tiroidea con o senza monitoraggio nervoso intraoperatorio

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SUMMARY

Intraoperative nerve monitoring (IONM) aimed at reducing the injuries of recurrent laryngeal nerve during thyroidectomy is controversial. We conducted a meta-analysis to assess the incidence of nerve injuries with or without IONM. Studies published from January 1994 to February 2012 in English language on humans were identified. Heterogeneity of studies was checked by the Higgins test. Summary estimates of predictive values of injury were made using the Mantel-Haenszel test based on the fixed-effects model. Publication bias was assessed by a funnel plot and Egger's method. Eight articles were selected accounting a total of 5257 nerves at risk. IONM revealed a significant impact in preventing transient injuries (positive predictive value = 5% [95% CI: 2-8], negative = 96% [95% CI: 91-100], relative risk = 0.73 [95% CI: 0.54-0.98], $p = 0.035$), whereas they failed to demonstrate effect on permanent injuries (positive predictive value = 2% [95% CI: 0.6-3.8], negative 99% [95% CI: 97-100], relative risk = 0.73 [95% CI: 0.44-1.23], $p = 0.235$). This meta-analysis demonstrated the merit of IONM in preventing transient injury during thyroidectomy. No advantage was found in permanent injuries.

KEY WORDS: Intraoperative neurostimulation • Recurrent laryngeal nerve • Thyroid surgery • Meta-analysis

RIASSUNTO

L'utilità del monitoraggio intraoperatorio dei nervi periferici (IONM), allo scopo di ridurre il danno dei nervi ricorrenti nel corso della chirurgia tiroidea, rappresenta ancora un aspetto controverso. Abbiamo, quindi, compiuto una metaanalisi, allo scopo di definire l'incidenza di danno nervoso con e senza IONM. Sono stati dapprima identificati gli studi eseguiti dal gennaio 1994 fino al febbraio 2012 in lingua inglese. L'eterogeneità degli studi presi in considerazione è stata valutata con il test di Higgins. Una valutazione complessiva del valore predittivo di danno è stata eseguita utilizzando il test di Mantel-Haenszel, basato sul modello effetti-fissi. Eventuali problemi legati alla pubblicazione sono stati valutati con un funnel plot e il metodo di Egger. Sono stati, alla fine, selezionati 8 lavori, per un numero complessivo di tronchi nervosi a rischio pari a 5.257. L'indagine ha mostrato un ruolo rilevante dello IONM nel prevenire danni nervosi transitori (valore predittivo positivo = 5% [95%CI:2-8], negativo = 96% [95%CI:91-100], rischio relativo = 0,73 [95%CI:0,54-0,98], $p = 0,035$), mentre non è stato possibile mettere in evidenza un effetto sul danno permanente [valore predittivo positivo = 2% (95%CI:0.6-3.8), negativo 99% (95%CI:97-100), rischio relativo = 0,73 (95%CI:0,44-1,23), $p = 0,235$]. La meta analisi ha dimostrato l'importanza dello IONM nel prevenire il danno nervoso transitorio durante la tiroidectomia, mentre non è stato possibile rendere evidente un suo ruolo per quanto riguarda il danno permanente.

PAROLE CHIAVE: Neurostimolazione intraoperatoria • Nervo laringeo ricorrente • Chirurgia tiroidea • Meta analisi

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Introduction

In thyroid surgery, optimal exposure of the gland and clear identification of anatomical structures are the cornerstone to enhance the patient safety. Many refinements have been introduced in recent decades, including the use of intraoperative nerve monitoring (IONM), which has the objective of lowering the incidence of thyroidectomy-associated hoarseness related to recurrent laryngeal nerve (RLN) injury. The incidence of RLN injury after thyroidectomy widely varies in the literature, ranging from 0.4% to 7.2% for temporary paresis and from 0% to 5.2% for permanent paralysis¹⁻³. This incidence is often underestimated because injury may be ignored or undetected at postoperative laryngeal examination. In addition, the risk of RLN injury is increased in patients with local malignancy, previous thyroid surgery, neck irradiation, substernal goiter or anatomic variability of the nerve.

IONM has gained widespread acceptance as an adjunct to the gold standard of visual nerve identification, and this technique can be used to distinguish both the RLN and external branch of the superior laryngeal nerve^{4,5}. However, it remains unclear whether IONM adds any value to the clinical outcome of thyroidectomy in terms of preserved individual voice performance. Uncertainty in the literature concerning the merits of IONM led us to conduct the present meta-analysis. The objective of the present study was to assess the risk of transient or permanent RLN injury in thyroid surgery performed with or without IONM.

Materials and methods

Methodology was developed from standard guidelines outlined in the Cochrane Handbook for Systematic Reviews of Intervention (version 5.1.0)⁶ and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement⁷.

Literature review

We performed a literature search using electronic search engines PubMed and Ovid, and the Cochrane Library database to identify all clinical trials published between January 1994 and February 2012 that included the words “neuromonitoring AND thyroid AND neck surgery, intraoperative neuromonitoring, intraoperative electrophysiological monitoring, IONM, recurrent laryngeal nerve monitoring”. The search was restricted to English-language literature and human subjects. We also checked the reference lists of all studies identified.

Inclusion criteria

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

- 1 Randomised prospective trials or retrospective studies comparing patients undergoing thyroidectomy with or without IONM;

- 2 Surgery including total, subtotal or near-total thyroidectomy and thyroid lobectomy in patients presenting with thyroid cancer or benign thyroid disease;
- 3 Description of primary data, results of IONM testing, and clinical outcomes;
- 4 Nerve monitoring performed using different methods;
- 5 Possibility of data extraction/calculation from the published results.

In case of overlap between patient populations, authors and centres, the trial with the largest number of patients was selected.

Data collection for analysis

The reviewers (FR and VA) independently selected studies and extracted the following data from each article: inclusion and exclusion criteria for patient selection, study design, patient characteristics (i.e. number, mean age, sex ratio), details of IONM assessment and study endpoints. Reported findings were defined as true positive in case of injury in the absence of IONM, and false positive in case of absence of injury with IONM. True negative was determined in patients without injury and without IONM, and false negative in patients with injury with IONM. The objective of the analysis was to assess the presence of either transient or permanent RLN injury. Any disagreement was resolved after discussion.

Statistical analysis

All analyses were performed using Stata/SE 12.0 statistical software (StataCorp, College Station, TX, USA). For each study selected data were presented as positive predictive value (PPV), which is the number of true positive/(number of true positive + number of false positive), and negative predictive value (NPV), number of true negative/(number of true negative + number of false negative). Risk ratio (RR) with 95% confidence intervals (CI) was also calculated to establish the usefulness of IONM for the prediction of transient and permanent injury after surgery. The Higgins test (I²) was performed to check the heterogeneity of the studies analysed. On the basis of this test, summary estimates of predictive values in terms of injury were made using the Mantel-Haenszel method, which is based on the fixed-effects model. Publication bias was assessed using a funnel plot and Egger's method. The relative contribution of each study to the meta-analysis was calculated according to the amount of information it contained, the number of nerves at risk and their variability. The influence of individual studies on the summary-effect estimate was evaluated using influence analysis. Any individual study suspected of having excessive influence, that is point estimate of its “omitted” analysis lying outside the confidence interval (CI) of “combined” analysis, was removed from the study. Meta-regression analysis was conducted to investigate whether the type of study (randomised or other) was associated with the treatment

effect. All analyses were performed for both transient and permanent RLN injuries. Statistical significance was set at $p < 0.05$. Unless otherwise specified, the p -value was considered to be 2-tailed.

Results

After excluding ineligible studies, eight articles were identified for full review⁸⁻¹⁵ (Fig. 1). One study was not considered in the meta-analysis on permanent injuries because of the absence of relevant events⁽¹²⁾. The eight studies selected included a total of 3029 patients with 5257 nerves at risk. The mean age of patients was 62 years (range 48–67 years), and the mean sex ratio was 3.76 (range 2.44–8.09). Table I details the characteristics of the

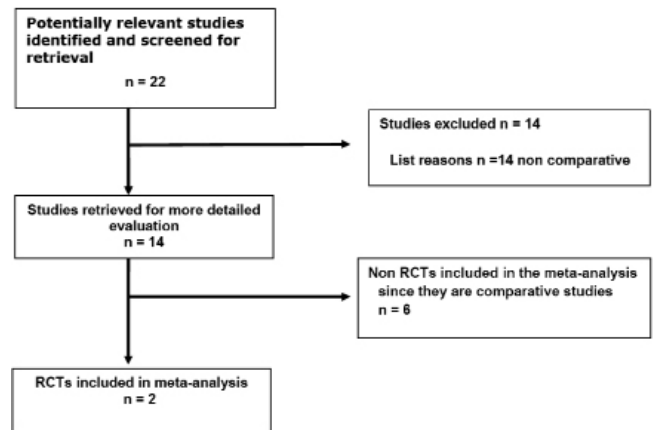


Fig. 1. Flow chart of the study.

Table I. Main demographic features of studies selected for meta-analysis.

Author Year	Type of study	Total patients	Total nerves at risk	Cancer	Men (%)
Atallah et al. 2009 (8)	Non-randomised	261	421	17	23.0
Barczyński et al. 2009 (9)	Randomised	1000	2000	60	9.06
Brauckhoff et al. 2002 (10)	Non-randomised	97	182	75	42.3
Chan et al. 2006 (11)	Non-randomised	639	1000	141	24.7
Dionigi et al. 2009 (12)	Randomised	72	224	44	13.9
Robertson et al. 2004 (13)	Non-randomised	165	236	78	22.9
Shindo & Chheda 2007 (14)	Non-randomised	684	1043	377	NA
Yarbrough et al. 2004 (15)	Non-randomised	111	151	76	36.9

NA = not applicable

Table II. Incidence of transient and permanent RLN injuries.

Author	Transient injuries (%)		Permanent injuries (%)	
	With IONM	Without IONM	With IONM	Without IONM
Atallah et al. 2009 (8)	8.8	9.1	3.9	3.8
Barczyński et al. 2009 (9)	1.9	3.8	0.8	1.2
Brauckhoff et al. 2002 (10)	1.89	4.55	0.0	2.27
Chan et al. 2006 (11)	3.4	4.0	0.8	1.2
Dionigi et al. 2009 (12)	2.7	8.3	0.0	0.0
Robertson et al. 2004 (13)	3.45	4.24	0.86	2.54
Shindo & Chheda 2007 (14)	2.09	2.96	1.64	1.61
Yarbrough et al. 2004 (15)	15.4	11.9	3.8	5.1

Table III. Positive predictive value (PPV), negative predictive value (NPV) and relative risk (RR) regarding transient and permanent injuries.

Author	Transient injuries			Permanent injuries		
	PPV% (95% CI)	NPV% (95% CI)	RR (95% CI)	PPV% (95% CI)	NPV% (95% CI)	RR (95% CI)
Atallah et al. (2009) (8)	5 (3-9)	95 (91-98)	0.92 (0.40-2.10)	4 (2-7)	96 (92-98)	1.00 (0.38-2.64)
Barczyński et al. (2009) (9)	4 (3-5)	98 (97-99)	0.50 (0.29-0.86)	1 (0-2)	99 (98-100)	0.67 (0.27-1.62)
Brauckhoff et al. (2002) (10)	2 (0-8)	99 (94-100)	0.43 (0.04-4.64)	1 (0-6)	100 (96-100)	0.29 (0.01-6.93)
Chan et al. (2006) (11)	4 (2-6)	97 (95-98)	0.85 (0.45-1.60)	1 (0-3)	99 (98-100)	0.66 (0.19-2.34)
Dionigi et al.* (2009) (12)	3 (0-7)	99 (95-100)	0.35 (0.04-3.27)	-	-	-
Robertson et al. (2004) (13)	4 (1-9)	97 (91-99)	0.83 (0.23-3.01)	3 (0-7)	99 (95-100)	0.34 (0.04-3.27)
Shindo & Chheda (2007) (14)	3 (1-5)	98 (97-99)	0.71 (0.32-1.54)	0 (0-1)	100 (99-100)	1.11 (0.10-12.19)
Yarbrough et al. (2004) (15)	1 (0-2)	83 (70-92)	1.28 (0.53-3.07)	5 (1-14)	96 (87-100)	0.76 (0.13-4.35)
Total meta-analysis	5 (2-8)	96 (91-100)	0.73 (0.54-0.98)	2 (0.6-3.8)	99 (97-100)	0.73 (0.44-1.23)

*Dionigi et al. was excluded for the absence of RLN permanent palsy

studies included in the meta-analysis. Table II shows the incidence of transient and permanent RLN injury with or without the use of IONM. Table III shows the PPV, NPV, RR and corresponding 95% CI for each study on transient and permanent injuries.

Transient injury

Overall results yielded by the Mantel-Haenszel method (fixed effect suggested by the heterogeneity test: $I^2 = 0.5\%$, $p = 0.708$) demonstrated a significant role of IONM in predicting RLN transient injuries: PPV was 5% (95% CI: 2–8) and the NPV was 96% (95% CI: 91–100), RR of 0.73 (95% CI: 0.54–0.98) with $p = 0.035$ (Fig. 2). Influence analysis was performed to identify studies with excessive influence (Fig. 3). The Begg test revealed that no bias was found in the publications used for the meta-analysis (Kendall's score, one-sided, $p = 1.000$). The type of study was not associated with the treatment effect ($p = 0.078$).

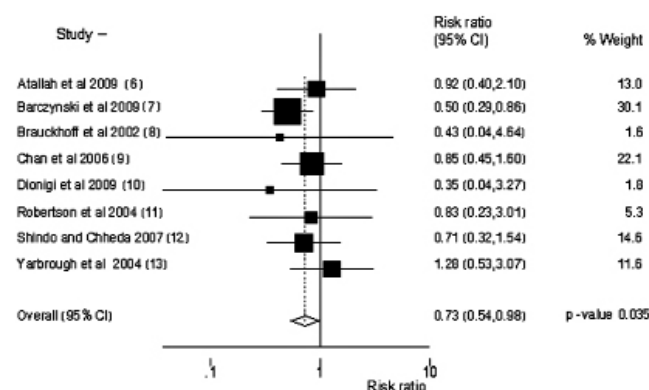


Fig. 2. Forest plot depicting the contribution (box area) and the relative risk of transient injury with/without IONM in each study included in the meta-analysis.

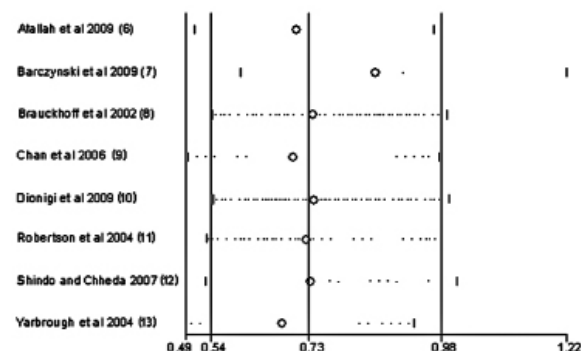


Fig. 3. Influence of transient injury with/without IONM in studies included in the meta-analysis.

Permanent injury

Permanent RLN injuries were not predictable by IONM as demonstrated by the overall results yielded by the Mantel-Haenszel method (fixed effect suggested by the

heterogeneity test: $I^2 = 4.2\%$, $p = 0.969$). The summary PPV was 2% (95% CI: 0.6–3.8) and the NPV was 99% (95% CI: 97–100) with a univariate RR of 0.73 (95% CI: 0.44–1.23) and $p = 0.235$ (Fig. 4). No study showed excessive influence as determined by influence analysis (Fig. 5). The Begg test revealed no publication bias, shown by Kendall's score (1-sided, $p = 0.548$). The type of study was not associated with the treatment effect ($p = 0.303$).

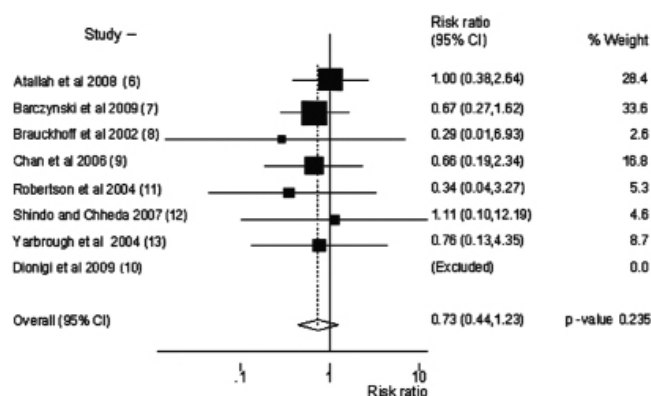


Fig. 4. Forest plot depicting the contribution (box area) and the relative risk of permanent injury with/without IONM in each study included in the meta-analysis.

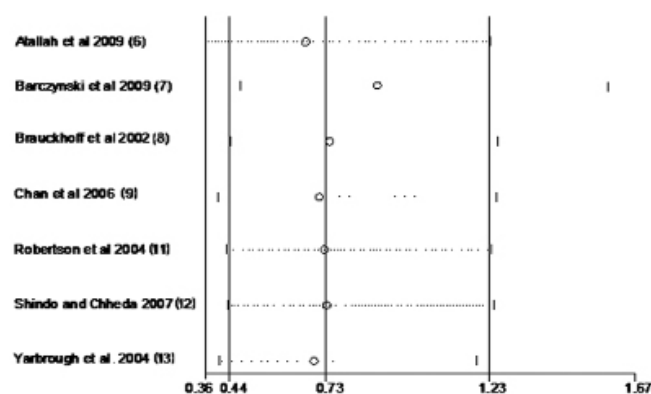


Fig. 5. Influence of permanent injury with/without IONM in studies included in the meta-analysis.

Discussion

RLN palsy is a serious complication after thyroid surgery leading, depending on its severity, to voice disorders, respiratory distress and aspiration¹⁶. Consequently, quality of life may be impacted, possibly prompting medico-legal litigation against the surgeon^{17,18}. During thyroidectomy, injury to the RLN may be a result of unintentional sectioning, stretching, thermal injury, entrapment by a ligature or ischaemia. Clear identification of the nerve by careful dissection, even in case of abnormal anatomy, is the best approach to avoid nerve trauma. IONM by electrical stimulation has been described and

proposed during thyroid surgery for more than four decades^{19,20}. It has the potential to enhance visual identification of the nerve, allowing more precise dissection and verification of its integrity, which minimises the risk of injury. A growing number of surgeons are using IONM in all cases of thyroid and parathyroid surgery, while others do so in selected patients considered at risk of RLN injury. However, many still do not use IONM, preferring direct visualisation. To the best of our knowledge, there is no overwhelming scientific evidence of its actual benefits in RLN preservation.

The current meta-analysis shows the impact of IONM on preventing transient RLN injury, but fails to demonstrate any effect on permanent palsy. This apparent discrepancy is related to the fact that transient injury occurs more frequently than permanent damage, and evolves in the majority of cases towards complete recovery and normal vocal cord function in the long term.

Although a beneficial effect of IONM in terms of lower incidence of transient and permanent nerve palsy has been suggested^{21,22}, many studies question its added value^{23,26}. The relationship between IONM and functional postoperative outcome has therefore proven to be less evident to define than expected, yielding a number of conflicting results. These discrepancies may be related to a relatively low PPV⁵. As the incidence of RLN palsy is low in experienced hands, to demonstrate the added value of IONM, one may postulate that inclusion of a large number of patients is needed. The current meta-analysis does not support this premise, however, as the positive contribution of IONM was observed in studies with no more than 2000 nerves at risk^{9,10}. It is also worth mentioning that in the largest multi-institutional prospective study evaluating a total of 16,448 consecutive thyroid procedures, IONM did not have any beneficial value compared to visual identification of RLN in the context of permanent paralysis²⁷. In this study, independent risk factors for permanent RLN paralysis included recurrent malignant or benign goiter, malignant disease, thyroid lobectomy, no nerve identification and low hospital or surgeon volume²⁷. It should be noted, however, that the latter study was removed from the current meta-analysis due to its overwhelming statistical weight and absence of data related to transient RLN palsy.

Controversies may be also related to poor uniformity of patient groups across different studies and lack of randomised controlled trials. Nerve injury risk during surgery for multinodular goiters is obviously lower than in case of surgery for large substernal masses growing in a restricted space, prior surgery due to fibrous tissue adhering firmly to the gland, surgery for thyroid cancer with lymph node dissection and recurrent malignancy with possible tumour infiltration of the nerve. For any given group of patients assessed by risk-group stratification, only prospective randomised controlled trials, pos-

sibly multicentre to reach a significant volume, have the potential to determine whether IONM achieves better results than direct identification of RLN by visual inspection. The individual performance of the surgeon has been shown to be the single most important factor related to postoperative outcome in case of surgery for "simple" benign goiters²⁸. In this context, nerve injury risk is almost nil in the hands of experienced surgeons, and there is no consistent need for IONM. By contrast, it was recently demonstrated that IONM improves outcomes of surgery for well differentiated thyroid cancer²⁷. In fact, the use of IONM helps to avoid the problem of remnant thyroid tissue during dissection at the level of Berry's ligament, where the RLN may be branched.

Although there is no global consensus on its value in every thyroid surgical procedure, IONM plays a key role in many circumstances that could aggravate the risk of nerve injury.

Indeed, the main benefit of IONM is its ability to guide the surgeon in the event of variations in the expected anatomic course of the inferior laryngeal nerve⁹, or in case of a non-recurrent inferior laryngeal nerve revealed by short latency, as recently demonstrated³⁰. The risk of nerve injury increases in patients with an anomalous RLN anatomy. Such variations include non-recurrence mainly on the right side^{31,32}, nerve displacement³³⁻³⁵ by thyroid nodularity or paratracheal lymphadenopathy, extralaryngeal branching of the RLN observed in 30% of patients³¹, and variations in the nerve course in relation to the inferior thyroid artery and Berry's ligament. In a recent analysis of RLN in 502 thyroid dissections, 60.8% of nerves were found to be in the expected tracheoesophageal groove position, while 4.9% were lateral and 28.3% were posterior to the trachea. Of greatest concern are cases where the RLN is located on the anterior surface of the thyroid gland (6%), which is a particularly high-risk area for nerve injury³⁶. IONM has also been shown to be helpful during minimal-access thyroid surgery procedures³⁷, including video-assisted thyroidectomy¹². As dissection is conducted in a narrow space, use of a stimulator helps to identify the plane of dissection and gives surgeons more confidence during surgery. However, benefits in terms of reduced postoperative morbidity were not demonstrated¹².

Despite the fact that the small number of included studies and lack of prospective randomised trials available for analysis limit the current meta-analysis, our results add new insights into the role of IONM during thyroidectomy, highlighting its merits in preventing transient injury. IONM methodology is a welcome adjunct to the surgical armamentarium, leading to better quality control during thyroid surgery. Further studies conducted according to international recommendations⁴ are nevertheless required to confirm these findings in populations with different risk factors.

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