JOURNAL OF SURGICAL RESEARCH 188 (2014) 152–161

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

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

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ARTICLE INFO

Article history:
Received 13 October 2013
Received in revised form
18 November 2013
Accepted 20 December 2013
Available online 25 December 2013

Keywords:
Thyroidectomy
Recurrent laryngeal nerve
RLN
Intraoperative neuromonitoring
IONM
Recurrent laryngeal nerve visualization
RLN VA
Recurrent laryngeal nerve palsy

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.

Part of this study was presented at the XVI Congress of the French Society of Endocrine Surgeons (AFCE-Association Francophone de Chirurgie Endocrinienne), Lyon, France, 14–15 June, 2013.

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http://dx.doi.org/10.1016/j.jss.2013.12.022

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