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MAIN ARTICLE

Value of intra-operative neuromonitoring of the recurrent laryngeal nerve in total thyroidectomy for benign goitre

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Abstract

Objective: This study aimed to evaluate the impact of intra-operative neuromonitoring of the recurrent laryngeal nerve during total thyroidectomy for benign goitre.

Methods: A single-centre retrospective study using historical controls was conducted for a 10-year period, comprising a series of 767 patients treated by total thyroidectomy for benign goitre. Of these, 306 had intra-operative neuromonitoring of the recurrent laryngeal nerve and 461 did not. Post-operative laryngeal mobility was assessed in all patients by direct laryngoscopy before hospital discharge and at post-operative follow-up visits.

Results: In all, 6 out of 461 patients (1.30 per cent) in the control group and 6 out of 306 patients (1.96 per cent) in the intra-operative neuromonitoring group developed permanent recurrent laryngeal nerve palsy. No statistically significant difference was observed between the two patient groups.

Conclusion: Intra-operative neuromonitoring does not appear to affect the post-operative recurrent laryngeal nerve palsy rate or to reliably predict post-operative recurrent laryngeal nerve palsy. However, it can accurately predict good nerve function after thyroidectomy.

Key words: Thyroid Gland; Complications; Recurrent Laryngeal Nerve Palsy; Laryngeal Nerve; Inferior; Intraoperative Neurophysiological Monitoring

Introduction

Total thyroidectomy is a common surgical procedure that is mainly performed for benign disease. Although hypocalcaemia is more frequent, the most serious post-operative complication of total thyroidectomy is recurrent laryngeal nerve (RLN) palsy. The latter can induce significant voice disorders, swallowing difficulties, respiratory disorders and serious social problems, especially when bilateral. Moreover, post-operative RLN palsy has been a frequent source of malpractice litigation following thyroid surgery over the last 20 years, notably in Germany.[1]

The main challenge in total thyroidectomy is to reduce the post-operative RLN palsy rate (especially for benign lesions) by minimising intra-operative RLN injury. This is therefore the main goal of intra-operative monitoring of the RLN during thyroid surgery.

Over the last 10–15 years, intra-operative neuromonitoring has become relatively well accepted as a useful accessory for localising and identifying the RLN, and for predicting post-operative laryngeal function at the end of the surgical procedure.[1–13] However, its ability to reduce the post-operative RLN palsy rate and the significance of intra-operative neurostimulation signals remain uncertain.[1–13]

Since 2005, intra-operative neuromonitoring has been systematically used during total thyroidectomy in our ENT and Head & Neck Department, regardless of surgical indications. This 10-year retrospective case–control study presents the results of our experience of performing intra-operative neuromonitoring in total thyroidectomy for benign lesions.

Materials and methods

This retrospective single-centre study using historical controls was based on a 10-year period from January 2001 to January 2010.

Ethical considerations

The study was approved by the Amiens University Medical Centre Institutional Review Board and conducted according to Evin's Law, which concerns ethical procedures in medical research in France.

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TABLE I
STUDY POPULATION AND SURGICAL INDICATIONS

Variable	All patients (n = 767)	Group 1: control (n = 461)	Group 2: IONM (n = 306)	p value
Main characteristics				
– Age (mean, median (years))	53, 53	53, 54	53, 53	>0.05
– Female (n (%))	630 (82.1)	383 (83.1)	247 (80.7)	>0.05
Surgical indications				
– Multinodular goitre (n (%))	435 (56.7)	263 (57.1)	172 (56.2)	>0.05
– Toxic goitre (n (%))	46 (6.0)	28 (6.0)	18 (5.9)	>0.05
– Cervicothoracic goitre (n (%))	122 (15.9)	77 (16.7)	45 (14.7)	>0.05
– Graves' disease (n (%))	104 (13.6)	54 (11.7)	50 (16.3)	>0.05
– Thyroiditis (n (%))	32 (4.2)	22 (4.8)	10 (3.3)	>0.05
– Secondary total thyroidectomy (n (%))	28 (3.7)	17 (3.7)	11 (3.6)	>0.05

IONM = intra-operative neuromonitoring

Population

The study cohort included 767 patients comprising 630 females and 137 males, with a mean age of 53 years (range 19–82 years) who underwent total thyroidectomy for benign thyroid disease.

Method

Patients of all ages and both sexes who underwent total thyroidectomy were included. The other inclusion criterion was the presence of benign thyroid disease such as multinodular goitre (including cervicothoracic goitre, toxic goitre and bilateral re-operations), Graves' disease or thyroiditis. Patients with thyroid cancer or previous external beam radiotherapy to the neck and those who had undergone unilateral thyroid lobectomy were not included.

All patients had undergone total thyroidectomy via a small neck incision under general anaesthesia. To prevent false positive responses in the neurostimulation test, no curare or muscle relaxant drugs were used. Neither sternotomy nor lymph node dissection along the RLN was performed. Thyroid lobectomies were performed in a caudocranial direction by capsular dissection after first identifying the RLN.

Since 2005, intra-operative neuromonitoring of the RLN (using a NeuroSign 400; Inomed, Teningen, Germany) has been systematically performed during total thyroidectomy at our institute. For this, the electrodes are imbedded in the laryngotracheal tube and stimulation is monopolar or bipolar. Identification of the RLN by neurostimulation is confirmed by an acoustic response. The neurostimulation test is considered positive when no acoustic response is obtained to an appropriate stimulus (that is, presumption of a non-functional nerve). The average neurostimulation intensity used was 1 mA.

Patients were divided into two groups: group 1 patients (control group) underwent surgery from 2001 to 2004 without intra-operative neuromonitoring; and group 2 patients underwent surgery from 2005 to 2010 with intra-operative neuromonitoring. All patients underwent early post-operative direct laryngoscopy (nasoendoscopy) before hospital discharge (usually on post-operative day two) and at the one-month post-operative follow-up visit. RLN was defined as complete immobility of the vocal fold and the arytenoid. All patients in whom post-operative RLN palsy was detected underwent immediate speech therapy. Patients with voice disorders or RLN palsy were regularly reviewed until their resolution or for up to one year. RLN palsy that persisted for one year after surgery was considered to be permanent.

Statistical analysis

Statistical analysis was performed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Data were expressed as the mean ± standard deviation, range or frequency, as appropriate. Between-group comparisons were performed using the chi-square test for categorical variables and the Student's t-test or Mann–Whitney test for continuous variables.

Results

A total of 767 patients were included in the study. Of these, 461 control patients underwent total thyroidectomy without intra-operative neuromonitoring (group 1) and 306 patients underwent total thyroidectomy with intra-operative neuromonitoring (group 2). Patient characteristics and surgical indications are presented in Table I.

No patient developed bilateral RLN palsy. In group 1, 6 out of 461 patients (1.30 per cent) developed permanent RLN palsy (i.e. 6 out of 922 RLNs; 0.65 per cent). In group 2, 6 out of 306 patients (1.96 per cent) developed permanent RLN palsy (i.e. 6 out of 612 RLNs = 0.98 per cent). There was no statistically significant difference between the two patient groups (Table II)

The diagnostic accuracy of intra-operative neuromonitoring for group 2 patients is shown in Table III. The sensitivity was 27.27 per cent and the positive predictive value was 10.52 per cent. The low sensitivity was due to false negative results in 6 out of 22 patients, and the low positive predictive value was due to false positive results in 6 out of 57 patients. Thus, in this case series, intra-operative neuromonitoring did not reliably predict post-operative RLN palsy. However,

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TABLE II
POST-OPERATIVE RLN PALSY RATES

Unilateral RLN palsy	Total (767 patients, 1534 nerves)	Group 1: control (461 patients, 922 nerves)	Group 2: IONM (306 patients, 612 nerves)	*p* value
Total (*n*)	46	24	22	>0.05
Transient (*n* (%))	34 (2.22)	18 (1.95)	16 (2.61)	>0.05
Permanent (*n* (%))	12 (0.78)	6 (0.65)	6 (0.98)	>0.05

IONM = intra-operative neuromonitoring; RLN = recurrent laryngeal nerve

the specificity was 91 per cent and the negative predictive value was 97.11 per cent (99.2 per cent for permanent RLN palsy). These data indicate that intra-operative neuromonitoring can confirm the anatomical integrity of the RLN after visual identification by dissection.

Discussion

To decrease selection bias and ensure homogeneity in surgical and neurostimulation techniques, this study was conducted at a single centre. Sampling variations in the two patient groups were purely random ($p > 0.05$). Both groups were comparable in that an increased rate of risk factors for post-operative RLN palsy (i.e. a higher proportion of cervicothoracic goitre or bilateral re-operations), which, could have artificially increased the post-operative RLN palsy rate independent of neurostimulation, was not found. Surgical indications were also similar to those reported in the literature, thus allowing the study results to be compared with those of similar published studies.[2–6]

The use of intra-operative neuromonitoring of the RLN during total thyroidectomy raises four questions. Does it decrease the risk of post-operative RLN palsy? Can it predict post-operative laryngeal function? Can it modify surgical management? What are the medico-legal considerations?

Most authors report a permanent post-operative RLN palsy rate after total thyroidectomy for benign disease of less than or equal to 1 per cent in terms of nerves (i.e. 2 per cent in terms of patients).[7,8] Our result of an RLN palsy rate of 0.78 per cent in terms of nerves is consistent with this.[7,8] The medical literature over the last 10–15 years generally indicates that intra-operative neuromonitoring during total thyroidectomy does not decrease the risk of permanent post-operative RLN palsy. In 2009, Barczyński *et al.* conducted a prospective, randomised, comparative study in 1000 patients (level of evidence, 1; grade of recommendation, A). They showed that intra-operative neuromonitoring of the RLN during total thyroidectomy decreased the risk of transient post-operative RLN palsy ($p < 0.007$), particularly in at-risk patients (including those with thyroid cancer, cervicothoracic goitre and re-operations).[2] However, these results remain controversial because of the relatively high rate of transient post-operative RLN palsy (5 per cent) in the group that underwent total thyroidectomy without intra-operative neuromonitoring of the RLN. Further, transient RLN palsy is not clinically significant; only permanent RLN palsy is clinically significant. The permanent post-operative RLN palsy rate did not differ between the two groups in the study by Barczyński *et al.*, indicating that intra-operative neuromonitoring of the RLN during total thyroidectomy had no impact on post-operative permanent RLN palsy.[2] In addition, Dralle *et al.*[3] and Chan *et al.*[4] conducted prospective comparative studies (level of evidence, 2a; grade of recommendation, B) and Shindo and Chheda[5] and Robertson *et al.*[6] conducted retrospective comparative studies (level of evidence, 2b; grade of recommendation, B). These authors all also concluded that intra-operative neuromonitoring of the RLN during total thyroidectomy did not decrease the post-operative RLN palsy rate, as confirmed by the present study. However, Dralle *et al.* considered that an accurate scientific evaluation of the impact of intra-operative RLN stimulation (based on the very low post-operative RLN palsy rate) would require 2 groups of 40 000 patients with thyroid cancer or 9 billion patients with benign thyroid disease.[8] It would be very difficult, if not impossible, to conduct such a large-scale multicentre study. However, it must be kept in mind that the absence of statistical significance owing to a lack of statistical power related to the low prevalence of post-operative RLN palsy cannot exclude the possible superiority of intra-operative neuromonitoring of the RLN *vs* visual identification of the RLN by dissection alone. In this case, the lack of evidence in favour of the use of intra-operative neuromonitoring of the RLN to

TABLE III
ACCURACY OF INTRA-OPERATIVE RLN STIMULATION FOR DETECTING POST-OPERATIVE RLN PALSY

Measure	RLN palsy		
	Total	Transient	Permanent
Sensitivity (95% CI)	0.2727 (0.0866–0.4588)	0.25 (0.0378–0.1312)	0.3333 (0–0.7105)
Specificity (95% CI)	0.9100 (0.8966–0.9342)	0.9127 (0.8898–0.9367)	0.9187 (0.8964–0.9419)
PPV (95% CI)	0.1052 (0–0.2334)	0.0730 (0–0.2005)	0.0400 (0–0.1968)
NPV (95% CI)	0.9711 (0.9570–0.9858)	0.978 (0.9655–0.9905)	0.992 (0.98447–0.996)

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; RLN = recurrent laryngeal nerve

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decrease post-operative RLN palsy rates may not correspond to evidence for a lack of efficacy.

In conclusion, in a study of 29 998 cases of RLN monitoring, Dralle *et al*. confirmed that intra-operative RLN stimulation did not significantly decrease the permanent post-operative RLN palsy rate and that RLN identification by dissection remains the 'gold standard' surgical technique to avoid RLN injuries.[8] However, Dralle *et al*.[3,8] and Hermann *et al*.[9] also considered that intra-operative RLN stimulation might help inexperienced surgeons (i.e. those who have performed less than 45 thyroidectomies) to more accurately identify the RLN during dissection, particularly in at-risk situations (cervicothoracic goitre, re-operations or Graves' disease). In our opinion, despite the risk of developing a 'technical addiction', intra-operative neuromonitoring of the RLN decreases the surgeon's level of stress during thyroid surgery, particularly when the RLN responds well to neurostimulation. However, the real significance of intra-operative responses to neurostimulation remains to be determined.

Our case series confirms the literature reports that intra-operative neuromonitoring of the RLN cannot reliably predict post-operative RLN palsy.[2–10] However, it can demonstrate anatomical integrity of the RLN after visual identification by dissection (i.e. it has a good negative predictive value of 99.2 per cent for permanent RLN palsy). Its main problem is the high rate of false negative and false positive signals, which cannot be ignored. For example, false negative signals can actually increase the RLN injury risk (even for post-operative RLN palsy) if surgeons exclusively rely on the monitoring system. False negative results can be easily explained by technical bias (e.g. defective equipment, poor electrode positioning, disconnection of cables during surgery) or user bias (e.g. stimulation of the wrong nerve, stimulation distal to a nerve lesion). From an electrophysiological perspective, acoustic and/or visual signals of neurostimulation are not scientifically reliable indicators of nerve function. The amplitude of the action potential is the more reliable electrophysiological parameter for assessing nerve function, i.e. intra-operative laryngeal electromyography (EMG) is more reliable than intra-operative RLN (or possibly vagus nerve) stimulation for predicting post-operative laryngeal function. Ideally, international reference measurements should be defined for the RLN and vagus nerve.[11] However, despite the lack of a significant link between the intra-operative neuromonitoring signal and RLN nerve function, many recent reports suggest that, when using intra-operative neuromonitoring in elective total thyroidectomy, loss of signal after the first lobectomy should lead to termination of the procedure to avoid the risk of post-operative bilateral RLN palsy. This is particularly the case for benign disease[1,12,13] (for which total thyroidectomy can theoretically be performed by two-stage procedures), but is also recommended for malignancies.[13] However, it may be difficult or even dangerous to the RLN to perform level VI lymph node dissection in the case of re-operation.

In contrast, in a recent prospective study of 290 patients, Sitges-Serra *et al*. concluded that 'after loss of signal of the RLN dissected initially, there was a 90 per cent chance of intra-operative signal recovery; in this setting, judicious bilateral thyroidectomy can be performed without risk of bilateral recurrent nerve paresis'.[10] However, in a retrospective study of litigation outcome following thyroid surgery, Dralle *et al*. noted that the use or non-use of intra-operative neuromonitoring has consistently been an issue in hearings since 2007. In the case of bilateral laryngeal palsy following total thyroidectomy, failure to implement neuromonitoring in compliance with international guidelines has led to a verdict against the surgeon in three-quarters of cases.[1] As suggested by Laccourreye and Chabolle, these findings may form the basis of new guidelines for benign thyroid surgery in Europe, or at least in Germany.[14] However, it is probable that all ENT surgery departments around the world that could use intra-operative neuromonitoring during thyroid surgery would benefit from such guidelines. In contrast, in a recent literature review, Sanabria stated that 'the literature shows inconsistencies in methodology, patient selection and randomisation in various published studies which may confound the conclusions of individual investigations. As routine use of neuromonitoring varies according to geography, its use should not be considered to be the standard of care.'

- **Post-operative recurrent laryngeal nerve palsy following thyroid surgery can be a source of malpractice litigation**
- **Intra-operative neuromonitoring might have a medicolegal impact**
- **Loss of signal after the first lobectomy should lead to termination of the procedure**
- **Intra-operative neuromonitoring can predict recurrent laryngeal nerve function after thyroidectomy**

Therefore, the value of intra-operative neuromonitoring remains controversial. In our experience, intra-operative neuromonitoring is a valuable surgical aid. Moreover, the fact that it confirms good post-operative laryngeal function in most cases clearly reassures surgeons when a good response to neurostimulation is obtained for both RLNs at the end of the procedure. Intra-operative neuromonitoring during thyroid surgery is also extremely useful in re-operations and for large cervicothoracic goitres, as the surgical procedure in these settings requires the initial identification of the RLN at the site of laryngeal penetration.[15] Intra-operative neuromonitoring is also useful for identifying and consequently preserving the external laryngeal nerve to avoid post-

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operative voice disorders. We believe that surgeons using intra-operative neuromonitoring during thyroid surgery should note the presence of weak neurostimulator signals and change their procedure in the case of unilateral signal loss during thyroidectomy, especially for benign disease. We believe that the risk of bilateral post-operative RLN palsy must be rigorously avoided for both benign lesions and malignancies, and particularly for non-aggressive follicular thyroid carcinomas.

Conclusion

There is ongoing debate concerning the impact and practical value of intra-operative neuromonitoring of the RLN during thyroid surgery for benign goitre. Our findings confirm published reports that intra-operative neuromonitoring of the RLN does not affect the post-operative RLN palsy rate and does not reliably predict post-operative RLN palsy. However, it can confirm the anatomical integrity of the RLN after visual identification by dissection. The non-use or poor use of intra-operative neuromonitoring in benign thyroid surgery could lead to medicolegal problems, and this must therefore be considered. Further prospective studies of intra-operative neuromonitoring of the RLN (laryngeal EMG) and the vagus nerve assessing electrophysiological and/or EMG data are also needed to clarify the relationship between intra-operative neurostimulation data and post-operative RLN function.

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