Randomized clinical trial

Randomized clinical trial of visualization *versus* neuromonitoring of recurrent laryngeal nerves during thyroidectomy

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Background: **The aim of this study was to test the hypothesis that identification of the recurrent laryngeal nerve (RLN) during thyroid surgery reduces injury, and that intraoperative nerve monitoring may be of additional benefit.**

Methods: **One thousand consenting patients scheduled to have bilateral thyroid surgery were randomized to standard protection or additional nerve monitoring. The primary outcome measure was prevalence of RLN injury.**

Results: **Of 1000 nerves at risk in each group, transient and permanent RLN injuries were found respectively in 38 and 12 nerves without RLN monitoring ($P = 0{\cdot}011$) and 19 and eight nerves with RLN monitoring ($P = 0{\cdot}368$). The prevalence of transient RLN paresis was lower in patients who had RLN monitoring by 2·9 per cent in high-risk patients ($P = 0{\cdot}011$) and 0·9 per cent in low-risk patients ($P = 0{\cdot}249$). The negative and positive predictive values of RLN monitoring in predicting postoperative vocal cord function were 98·9 and 37·8 per cent respectively.**

Conclusion: **Nerve monitoring decreased the incidence of transient but not permanent RLN paresis compared with visualization alone, particularly in high-risk patients. Registration number: NCT00661024 (http://www.clinicaltrials.gov).**

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Introduction

Apart from hypoparathyroidism, dysfunction of the recurrent laryngeal nerve (RLN) is the most common complication of thyroid surgery. Voice impairment diminishes quality of life, and often leads to litigation[1]. The incidence of RLN palsy varies from less than 1 per cent to as high as 20 per cent, depending on the type of disease (benign or malignant), the type of thyroid resection (first-time or reoperation) and the extent (subtotal or total thyroidectomy), the surgical technique (with or without routine RLN identification) and surgeon experience[2–8].

In 1938, Lahey reported a significantly lower incidence of RLN injury following thyroidectomy with clear visualization of the nerves than after operation without nerve identification[2]. Since then, many prospective studies have confirmed this observation, advocating routine RLN identification as the 'gold standard' in safe thyroid surgery[3–8]. But even in the most experienced hands RLN palsy occurs occasionally, with a typical frequency of less than 1 per cent, owing to variability in RLN anatomy and difficulties in nerve identification under challenging conditions, such as advanced malignancy or reoperative surgery.

Recent studies have shown that intraoperative neuromonitoring can aid RLN identification[9–14]. However, its role in reducing the frequency of RLN injury and the value of predicting postoperative RLN function remain controversial. Only a few series have level III evidence and grade C recommendation according to evidence-based criteria (Sackett's classification, modified by Heinrich)[11,15–20]. Large prospective randomized trials addressing these issues are scarce because of the large numbers of patients needed (more than 7000 per arm) to reach the appropriate power. The present medium-sized, single-centre, prospective randomized study compared the frequency of transient RLN paresis after surgery with RLN visualization alone and with intraoperative nerve monitoring.

Methods

A total of 1488 patients were referred to the Department of Endocrine Surgery, Jagiellonian University College of Medicine, Krakow, Poland, for first-time thyroid surgery between January 2006 and June 2007. Of these, 1013 were eligible for the study (*Fig. 1*). The inclusion criterion was bilateral neck surgery. Exclusion criteria included previous thyroid or parathyroid surgery, unilateral thyroid pathology eligible for a minimally invasive approach, mediastinal goitre, preoperative RLN palsy, pregnancy or lactation, age less than 18 years, American Society of Anesthesiologists grade 4 and inability to comply with the follow-up protocol.

Patients were randomized to two equal groups of 500 (*Table 1*), to have RLNs identified by visualization alone or with intraoperative nerve monitoring during surgery. Randomization was performed by computer-generated permuted block sequencing and allocated using sealed envelopes to be opened in the operating theatre.

Each group had 1000 RLNs at risk. Patients were blinded to their group assignment. The primary endpoint was RLN injury events; secondary endpoints included the utility of neuromonitoring in identifying RLN anatomical variations and predicting postoperative vocal cord dysfunction.

The study was approved by the Bioethics Committee of the Jagiellonian University.

Two anaesthetists followed a strict protocol, including intravenous midazolam premedication, induction with fentanyl, thiopental and suxamethonium, endotracheal intubation and sevoflurane maintenance. No other muscle relaxants were used during the operation.

Surgical technique

All operations were performed by the three authors, experienced endocrine surgeons, with a standard Kocher's skin incision. The thyroid resections performed are presented in *Table 1*. In each patient, the RLNs were exposed, and the branches of the superior and inferior thyroid arteries were divided close to the thyroid capsule (peripheral ligation). RLNs were routinely identified by visualization, and half of the patients had additional nerve monitoring with the Neurosign® 100 system (Inomed, Teningen, Germany). After identification of the cricoid and thyroid cartilage, the ipsilateral vocal muscle was impaled with the bipolar recording electrode through the cricothyroid ligament. The neutral electrode was placed in the sternocleidomastoid muscle. The proper placement of the electrodes was confirmed by an impedance meter of the circuit in the patient in the final operating position. Before any manipulation of the thyroid gland, the vagus

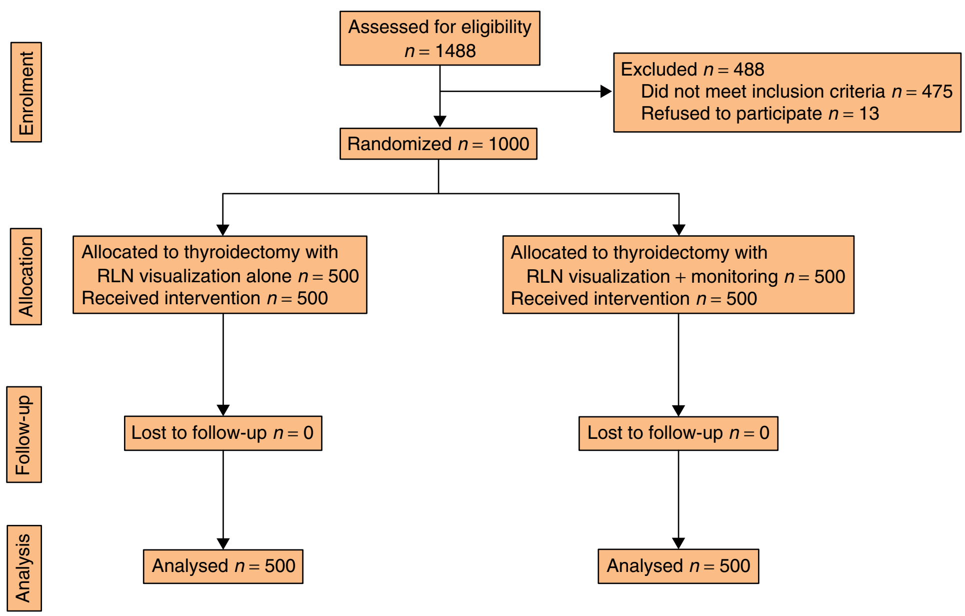

Fig. 1 Study flow chart. RLN, recurrent laryngeal nerve

Table 1 Demographic data, indications for surgery and selected operative details

	RLN visualization alone ($n = 500$)	RLN visualization + monitoring ($n = 500$)	P‡
No. of RLNs at risk	1000	1000	
Age (years)*	51·9(14·7)	51·3(14·4)	0·471§
Sex ratio (F : M)	10·7 : 1·0	10·1 : 1·0	0·756
Disease			
Non-toxic nodular goitre	350 (70·0)	346 (69·2)	0·783
Thyroid carcinoma	60 (12·0)	62 (12·4)	0·846
Grave's disease	32 (6·4)	28 (5·6)	0·594
Toxic nodular goitre	50 (10·0)	54 (10·8)	0·678
Thyroiditis	8 (1·6)	10 (2·0)	0·634
Procedure			
Total thyroidectomy	371 (74·2)	378 (75·6)	0·609
Dunhill operation†	101 (20·2)	96 (19·2)	0·690
Bilateral subtotal thyroidectomy	28 (5·6)	26 (5·2)	0·779
Central compartment clearance	58 (11·6)	59 (11·8)	0·921
Lateral neck dissection	12 (2·4)	15 (3·0)	0·558
Retrosternal goitre	79 (15·8)	83 (16·6)	0·730
Giant goitre (> 300 g)	21 (4·2)	19 (3·8)	0·746
Operating time (min)*	95·7(24·7)	104·8(26·7)	< 0·001§
Estimated blood loss (ml)*	55·4(54·4)	55·5(49·7)	0·287§
Weight of specimens (g)*	55·0(44·0)	54·8(42·6)	0·459§

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Unilateral thyroid lobectomy and contralateral subtotal thyroid resection. RLN, recurrent laryngeal nerve. ‡χ^2 test unless indicated otherwise; §Student's t test.

nerve was first dissected over a short stretch to allow for the initial assessment of the indirect stimulation response. A handheld bipolar, concentric stimulating probe was used with a current amplitude of 1 (range 0·5–1·5) mA (depending on the RLN threshold) and 3-Hz impulses of 200 ms each for 1–2 s. The electrical field response of the muscle was documented as an acoustic signal. An attempt was made to identify the RLNs by using the electrode before their visualization rather than by palpation or surgical dissection. After the removal of the thyroid lobe, both direct stimulation (through an electrode placed on the ipsilateral RLN nerve) and indirect stimulation (through an electrode placed on the ipsilateral vagus nerve) responses were determined. These final stimulation responses were used for predicting the postoperative outcome. The 'laryngeal twitch response' was not evaluated routinely.

The validity of nerve monitoring was defined and calculated according to Chan and Lo[19]. A missing signal was considered positive, predicting postoperative ipsilateral vocal cord injury. The test result was regarded as true positive when ipsilateral RLN paresis was confirmed on postoperative laryngoscopic examination and false positive when normal ipsilateral vocal cord function was found. An intact signal after the thyroidectomy was considered negative, predicting normal postoperative vocal cord function. This was interpreted as true negative if there was normal ipsilateral vocal cord function and false negative if there was a postoperative laryngoscopic diagnosis of RLN paresis.

Perioperative management and follow-up

Indirect laryngoscopy by a throat specialist was mandatory before surgery and on day 2 after surgery. In patients with RLN paresis, an additional examination was scheduled at 2 weeks and 1, 2, 4, 6 and 12 months after surgery, or until the vocal cord function recovered. Vocal cord paresis for more than 12 months after the operation was regarded as permanent palsy.

Statistical analysis

The sample size was estimated based on the principle of detecting a 2 per cent difference in the incidence of transient RLN injury with a 90 per cent probability at $P < 0.050$. The incidence of nerve paresis was calculated based on the number of nerves at risk. The analysis of both primary and secondary outcomes was performed on an intention-to-treat basis. The significance of categorical variables was evaluated with the χ^2 test, and the unpaired Student's t test was used for continuous variables (STATISTICA™; StatSoft, Katowice, Poland). All the data were entered into a dedicated spreadsheet (Microsoft

Excel® 2002; Microsoft, San Jose, California, USA) by a medical assistant and analysed by a statistician. $P < 0.050$ was considered significant.

Results

Primary endpoint analysis

In operations with RLN visualization plus additional nerve monitoring, the prevalence of RLN injury, transient RLN paresis and permanent RLN palsy was respectively 2·3 per cent ($P = 0.007$), 1·9 per cent ($P = 0.011$) and 0·4 per cent ($P = 0.368$) lower than with visualization alone. At 12-month follow-up, 38 of 50 patients (76·0 per cent) having visualization alone *versus* 19 of 27 (70·4 per cent) having additional monitoring recovered their vocal cord function (median 4 (range 1–6) months after surgery). Further analysis of patients stratified according to risk of RLN injury revealed 3·4 per cent lower overall RLN morbidity in low-risk *versus* high-risk patients without additional nerve monitoring ($P = 0.014$), and 3·7 per cent lower overall RLN morbidity ($P = 0.005$) and 2·9 per cent lower transient RLN morbidity ($P = 0.011$) in high-risk patients operated on with *versus* without additional monitoring (*Table 2*). In all low-risk patients, both overall and transient RLN morbidity rates were 0·9 per cent lower after surgery with additional nerve monitoring than with visualization alone ($P = 0.249$).

Secondary endpoint analysis

Nerve stimulation allowed localization of 137 (13·7 per cent) of the RLN nerves before visual nerve exposition and 92 (9·2 per cent) more bifurcated nerves than RLN visualization alone. This difference was significant for bifurcations close to Berry's ligament and near the inferior thyroid artery (*Table 3*). The value of nerve monitoring in predicting postoperative vocal cord function was unequivocal. Indirect RLN stimulation through the vagus nerve after thyroidectomy was more accurate than direct stimulation of RLN. Indirect RLN stimulation was more sensitive in high-risk than low-risk patients,

Table 2 Prevalence of recurrent laryngeal nerve injuries at postoperative laryngosopy stratified according to risk

	RLN visualization alone			RLN visualization + monitoring			
	Low risk ($n = 508$)	High risk ($n = 492$)	*P* value*	Low risk ($n = 494$)	High risk ($n = 506$)	*P**	*P* value†
Paresis							
Transient	14 (2·8)	24 (4·9)	0·080	9 (1·8)	10 (2·0)‡	0·858	0·011
Permanent	3 (0·6)	9 (1·8)	0·072	3 (0·6)	5 (1·0)	0·499	0·368
Overall	17 (3·3)	33 (6·7)	0·014	12 (2·4)	15 (3·0)§	0·601	0·007
Total	50 (5·0)			27 (2·7)			0·007

Values in parentheses are percentages. Low-risk group, surgery for non-toxic goitre without retrosternal extension; high-risk group, surgery for cancer including central lymph node clearance, thyrotoxicosis, retrosternal or giant goitre, thyroiditis. RLN, recurrent laryngeal nerve. *Low-risk *versus* high-risk patients; †RLN visualization alone *versus* RLN visualization plus monitoring; ‡§$P = 0.011$, §$P = 0.005$ *versus* high-risk patients having RLN visualization alone (other subgroup differences were not significant) (χ^2 test).

Table 3 Anatomical variations of recurrent laryngeal nerve

	RLN visualization alone	RLN visualization + monitoring	Monitoring added value†	*P* value‡
No. of RLNs at risk*	1000	1000		
One trunk	73.5 (735)	63.8 (638)		< 0·001
Bifurcation < 0·5 cm from entry into larynx	16.8 (168)	19.6 (196)	2·8	0·104
Bifurcation close to Berry's ligament	6.4 (64)	11.2 (112)	4·8	< 0·001
Bifurcation near inferior thyroid artery	1.4 (14)	3.0 (30)	1·6	0·014
Non-recurrent laryngeal nerve	0.2 (1)	0.8 (4)	0·6	0·176
RLN identification rate	99.4 (994)	99.7 (997)	9·8	0·316

Values are percentages (actual numbers in parentheses); *actual numbers. †Difference between the number of bifurcated recurrent laryngeal nerves (RLNs) identified during thyroidectomy with visualization plus nerve monitoring and number identified by visualization alone, expressed as a percentage of nerves at risk (for non-recurrent laryngeal nerves, values were calculated for patients, not for nerves at risk). ‡χ^2 test.

Table 4 Validation of nerve monitoring for predicting postoperative recurrent laryngeal nerve function stratified according to risk

	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Indirect RLN stimulation*					
Low risk	53·8	97·1	33·3	98·5	96·0
High risk	71·4	97·1	35·7	99·1	96·4
Overall	63·0	97·1	37·8	98·9	96·2
Direct RLN stimulation					
Overall	44·4	96·4	25·5	98·4	95·0

*Through vagus nerve after thyroid resection. PPV, positive predictive value; NPV, negative predictive value; RLN, recurrent laryngeal nerve.

but the positive predictive value (PPV) value remained low (*Table 4*). The mean operating time was longer by 9·1 min for thyroidectomies using nerve monitoring. Technical problems occurred in 24 operations leading to the nerve monitoring signal being lost, but it was restored immediately after the setup check (dislodged grounding wires in 14 operations and bipolar electrode displacement in ten). No serious complications were observed from needle electrodes being inserted into the vocal muscles through the cricothyroid ligament.

Minor complications included endotracheal tube cuff puncture requiring reintubation (in three patients) and a small vocal cord haematoma (two).

Discussion

In this study, thyroid operations using RLN monitoring had transient and permanent RLN injury rates of 1·9 and 0·8 per cent respectively, and those using visualization alone had rates of 3·8 and 1·2 per cent respectively. The prevalence of transient RLN paresis was lower in patients who had RLN monitoring by 2·9 per cent in high-risk patients and 0·9 per cent in low-risk patients.

Improved thyroid surgery outcomes with RLN monitoring have been documented in few non-randomized studies[15,18,21]. Dralle and colleagues[18] reported on the risk factors for vocal cord paresis with visualization and nerve monitoring compared with visual or no RLN identification in 29 998 nerves at risk. For less experienced surgeons, nerve monitoring resulted in a reduced rate of permanent RLN palsy. Experienced thyroid surgeons achieve a very low RLN morbidity rate following first-time surgery for benign goitre (less than 1 per cent), leaving a narrow space for improvement by nerve monitoring. However, in many challenging thyroid operations (thyroid malignancy, toxic or recurrent goitre), there is much more room for improvement (1–10 per cent) and even experienced surgeons may expect benefit from nerve monitoring[16]. Unfortunately, a prospective, randomized, two-arm and multicentre study is difficult to perform after the German experience, as many patients and surgeons expect nerve monitoring to provide additional benefits, thus limiting randomization to a non-monitored control group[18].

The present study is the first reported two-way randomization between differing RLN protection techniques using nerve monitoring in one of the arms. The power of this study focused on the prevalence of transient RLN paresis for two reasons. First, RLN paresis occurrence diminishes the quality of life for a few weeks to months after thyroid surgery; any improvement in this field is welcome. Second, owing to an association between the incidence of vocal cord malfunction diagnosed after surgery and permanent nerve palsy (reported recovery rate about 70–80 per cent), a significant decrease in the prevalence of RLN paresis achieved with nerve monitoring could bring later benefits as well.

A major benefit of RLN monitoring is assistance in nerve identification, resulting in a significant decrease in the prevalence of RLN temporary paresis (*Table 2*). Repetitive tissue stimulation in the vicinity of the nerve can aid the dissection, allowing for nerve localization with a stimulation probe before visual identification. Some anatomic variants of RLN are at an increased risk of injury. The incidence of RLN bifurcations and anastomoses over 0·5 cm inferiorly to the cricoid cartilage was reported by Katz and Nemiroff[22] as 63 per cent of 1177 visualized nerves. However, in most studies, the RLN branching rate does not exceed 30 per cent, which suggests underestimation due to difficulties in visual identification. In the present study, nerve monitoring helped to identify 33 per cent more RLN bifurcations than visualization alone. A bifurcated RLN is particularly prone to injury near the inferior thyroid artery or ligament of Berry. The posterior sensory branch may be mistaken for the entire RLN, causing the injury of the anterior motor branch. Nerve monitoring was able to help by confirming the location of the motor component of the RLN.

The sensitivity of vagal stimulation at the end of surgery was 63·0 per cent in this study, meaning that almost two of three nerve pareses were predicted during surgery. The PPV was 37·8 per cent, so that almost two-thirds of missing signals were caused by reasons other than RLN paresis. A low PPV for nerve monitoring has also been reported in other studies[18,19,23–26], because of a relatively low prevalence of RLN palsy and a higher false-positive rate (owing to technical errors, such as detachment or displacement of the electrodes). Theoretically, the PPV of nerve monitoring could have been low in this study partly because laryngoscopy was performed on the second instead of the first postoperative day. Indeed, more importantly, the validity of a missing acoustic signal in nerve monitoring could be altered by a detailed electromyographic analysis of the latency and amplitude changes of the revoked potentials after thyroid resection compared with preoperative values. Previous reports have demonstrated that a decrease in amplitude greater than 50 per cent or a latency time more than 20 per cent longer predict postoperative RLN dysfunction[25]. Although the present nerve monitoring system based only on acoustic signal monitoring allowed for no quantitative analysis, it was used with good previous experience supported by cost-effectiveness validation[13]. Both specificity and negative predictive value (NPV) of nerve monitoring were high in this study, similar to other reports[18,19,23–25]. However, NPV reliability was limited by an almost 3 per cent chance of vocal cord paresis where there was an intact monitoring signal.

So what are the potential clinical implications of RLN monitoring predictive values? A missing monitoring signal after the first thyroid lobe resection may discourage surgeons from performing one-stage bilateral resections or limit the planned extent of the contralateral thyroid lobe resection, particularly in benign goitre. However, owing to the low PPV of the method, only a third of patients would benefit from avoiding the risk of bilateral vocal cord palsy, whereas the remaining two-thirds can expect normal vocal cord function after surgery. Such patients may require unnecessary second-stage operations for contralateral completion. On the other hand, in accordance with a high NPV, patients with intact monitoring signals and vocal cord paresis found on postoperative laryngoscopy have a great chance of improvement. This argument of a good prognosis can be used in discussion with such patients[11].

Visual RLN identification remains the 'gold standard' for nerve protection, and it is up to each surgeon to decide whether to use nerve monitoring as a routine adjunct to each thyroid operation or to reserve it for challenging operations. But only good understanding of the electrophysiological background of the nerve monitoring method and daily practice in uncomplicated operations allows mastery of this novel technique. RLN monitoring also allows for nerve function documentation before and after thyroid resection (by printing the electromyographic signal of evoked potentials), which is of great importance in an increasing number of litigations[11,12].

A major drawback of this study is inadequate power to evaluate reliably the reported 33 per cent decrease in permanent RLN palsy prevalence with nerve monitoring. However, based on the results of the present investigation, a sample of 2500 patients in each arm would be needed to find a significant difference in permanent RLN palsy of 0·4 per cent of nerves at risk (from 1·2 to 0·8 per cent) with 95 per cent probability. This is a much smaller sample than the previously suggested 7000 patients per arm to indicate the significance of a 0·2 per cent difference (from 0·5 to 0·3 per cent of nerves at risk).

The second weak point is that the nerve monitoring analysis was based on the acoustic signal alone, with no further evaluation of electromyographic parameters. A detailed analysis of post-thyroidectomy changes in latency and amplitude of the electromyographic signals could be reviewed to develop more accurate interpretation criteria.

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