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Impact of continuous intraoperative vagus stimulation on intraoperative decision making in favor of or against bilateral surgery in benign goiter

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The advent of continuous vagus stimulation (CVS), eliminating lag time between nerve preparation with potential trauma and stimulation, has transformed the intraoperative surgical strategy in thyroid surgery. Continuous intraoperative nerve monitoring empowers the surgeon to be optimally aware of traction-related injury to the recurrent laryngeal nerve (RLN). Electromyographic precursor lesions, called combined events, prompt surgeons to cease harmful surgical maneuvers and release the nerve before

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damage to the nerve is established. Complete RLN recovery, defined as restitution of the nerve amplitude to ≥50% of baseline, assures the surgeon that it is safe to pursue completion surgery of the contralateral side in one procedure. If this restitution is incomplete or absent (<50% of amplitude baseline) immediate vocal cord paralysis is likely and it is advisable to delay completion surgery until the nerve has fully recovered.
This review summarizes the tremendous progress made in this dynamic field, delineating the extent to which CVS has changed the landscape: tailoring intraoperative decision making to determine the safest course of action for patients with benign goiter.

Introduction

For half a century, risk minimization, the process of reducing a risk exposure towards zero, has been one of the core elements of thyroid surgery especially as it relates to perhaps the most calamitous of thyroid surgery complications, bilateral vocal cord paralysis. As Riddell stated in the 1970's: "*It is the author's inflexible rule never to resect the second lobe of the thyroid in a bilateral procedure until the integrity of the recurrent nerve on one side has been proven*." [1] Without having information about the functional integrity of the recurrent laryngeal nerve (RLN) at one's fingertips, adherence to this fundamental surgical principle has been challenging. Intraoperative neural monitoring (IONM), affording functional surveillance across the entire vagus-RLN axis, has closed most, if not all of that gap [2]. Intraoperative nerve electrophysiology has been used as a surrogate parameter portending clinical outcome, specifically voice, breathing and swallowing. Impairment of any of these important clinical functions impacts postoperative health-related quality of life [3]. One-sided RLN paralysis can cause dysphagia, hoarseness, and aspiration with its attendant respiratory problems. More serious is the paralysis of both RLNs, estimated at 0.4% [4], which compromises patency of the airway and, if severe, may enforce tracheostomy to avoid suffocation [5].

Integration of IONM into surgical practice obviates bilateral vocal cord paralysis under the premise that completion surgery of the other side is postponed after definitive loss of the EMG signal (LOS) on the first side of resection [6–8]. This notion prompted 93.5% of German surgeons who used IONM and responded to a nationwide 2011 questionnaire survey to convert a planned one-stage bilateral procedure into a two-stage procedure after LOS on the first side of resection [9]. Similarly, a 2009–2013 analysis of 1757 patients on the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery supported the idea of staged thyroidectomy after LOS on the first side of resection [10].

Because intraoperative LOS recorded on intermittent IONM is not followed by vocal cord paralysis in up to one-third of patients, the concept of two-staged completion surgery has been called into debate [11,12]. For instance, the majority of surgeons who completed the online questionnaire of the French Association of Endocrine Surgeons stated that they continued bilateral thyroidectomy according to plan despite LOS on the first side of resection [13]. Inexperience with IONM and/or lack of awareness of the International Neural Monitoring Study Group (INMSG) recommendations [14], were underlying these decisions. A recent report from Spain advocated one-stage contralateral thyroidectomy in the face of definitive LOS during resection of the first side, avoiding the expense, psychological burden and potential complications of a second procedure [15].

This conflicting information illustrates the difficulty of conveying the benefits of IONM. As found previously, the primary ethical and medicolegal issues raised by neural monitoring relate to yet unproven benefit of raising high expectations of utmost patient safety against not utilizing the technology to gain superior information for patient care decision making [16]. Application of CVS is proficient to solve quandaries of IONM as it enables identification of "combined events", the progression of which must be avoided if RLN integrity is to be preserved [3,17–24]. Given the recent quantum leap in the field of IONM, it is pertinent to review the current body of evidence to determine the safest course of action for a given patient requiring bilateral thyroid resection.

Prerequisites for CVS

Evaluation of vocal cord movement

For correct interpretation, intraoperative EMG findings need to be correlated with vocal cord function. Laryngoscopy forms an integral part of the preoperative work-up for thyroid surgery [22]. Visual lack of vocal cord activity needs to be interpreted with caution because some nerves, despite generating proper EMG signals, may not recruit enough muscle fibers to provide for gross vocal cord motion [25].

Concept of the dominant side

The dominant side in planned bilateral thyroid surgery, by implication, is the larger lobe, or the lobe harboring the suspected or proven lesion or hyperfunctioning nodule, denominating the indication to surgery. In the context of multinodular goiter, the dominant lobe typically is not only larger but also holds more nodules. Starting the resection on the dominant side is directed at the leading thyroid pathology responsible for the majority of symptoms [26,27].

Informed consent

As for management of their disease, patients take a keen interest in shared decision-making [28]. Patient autonomy mandates that the informed consent form specify the use of CVS and clarify the need for a staged procedure in the event of LOS on the first side of resection [9,29,30]. This entails explanation of the limitations inherent in IONM, in particular when a bilateral thyroid operation planned.

Technical issues and standards

For CVS, a stimulation electrode is placed on the vagus nerve (Fig. 1) [3,17,31]. For recording of EMG signals, multichannel EMG systems, EMG displays, and sensing endotracheal surface electrodes are used. All manufacturers (Medtronic, Jacksonville, USA; inomed, Emmendingen, Germany; Dr. Langer Medical, Waldkirch, Germany) offer commercial neural monitoring equipment, which differ in how the EMG is displayed, how alarm limits are set, and how vagus electrodes are configured. The additional use of hand-held stimulation probes aids in identifying the RLN and tracking its anatomical course.

The following points need to be taken into account in order to obtaining meaningful EMG signals:

- Collar incision, ranging from small incisions to extended Kocher incisions.
- Opening of the carotid sheath and identification of the vagus nerve, before exposing the thyroid gland through an anterior (midline) or lateral (between the sternohyoid and sternocleidomastoid muscles) approach. The midline approach is adequate for small benign goiters, whereas the lateral approach, yielding greater exposure, is more suited for large goiters and reoperations. When the electric wires can be kept outside the operative field, the risk of inadvertent dislocation of the vagus electrode is greatly diminished.
- Morphological and functional check of the vagus nerve using the hand-held stimulation probe before fastening the CVS electrode on the nerve. When stimulation is unsuccessful, the troubleshooting algorithm for IONM [2] needs to be adhered to. The right vagus nerve should be stimulated further down the neck to exclude presence of a non-recurrent inferior laryngeal nerve (<1%) [32].
- Circumferential dissection of a short segment of the vagus nerve while preserving its blood supply (Fig. 1A).
- Resting of the CVS electrode on the vagus nerve (Fig. 1B–D) with initial stimulation at 1 mA and 1 Hz.

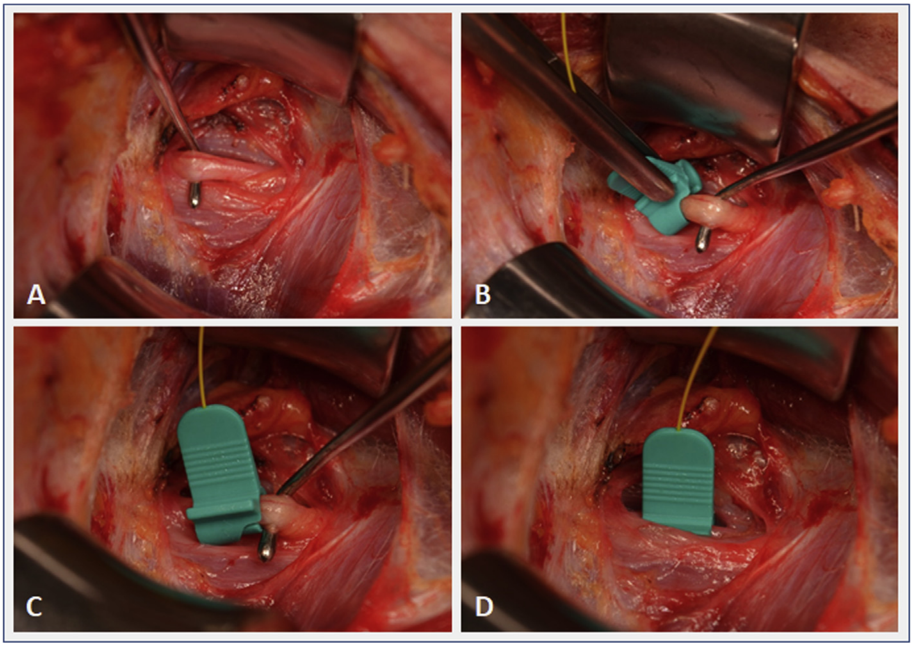

Fig. 1. Placement of a monopolar Automatic Periodic Stimulation (APS®) electrode on the vagus nerve. A. Retraction of the vagus nerve after circular dissection of a short nerve segment. B. Resting of the APS® electrode on the nerve, with an anatomic forceps keeping the enclosure tabs open. C. Released APS® electrode on the vagal nerve which is held in position by a retractor. D. APS® electrode resting on the vagal nerve inside the carotid sheath.

- Calibration of the IONM system. For stable and reliable EMG signals, the baseline amplitude must reach ≧500 μV [17]. To optimize sensitivity for impending nerve injury, the baseline amplitude should be maximized.
- Start CVS. All subsequent EMG changes are gauged against the calibrated amplitude and latency baselines and graphically displayed on the monitor screen as a function of time. Acoustic and optical alerts can also be defined at thresholds signaling approach of imminent nerve injury and demanding release of the distressed nerve [23].

In children aged ≤6 years, the unavailability of suitable size commercial electrodes limits the use of circumferential clip and tube surface electrodes [33]. Moistened gauze pads can be useful to connect a small vagus nerve to a larger circumferential clip electrode by snugging the former against the latter. An experienced consultant anesthesiologist can fasten a surface electrode pad on a size 3.5 mm endotracheal tube. In this situation, the surface electrode pad must be trimmed carefully to prevent it from overlapping and malfunctioning [33].

Safety

Only a few IONM studies report adverse events, and if so, these events were mostly unrelated to intraoperative nerve stimulation with stimulation at the low frequencies used at 1 or 2 mA [3,34–37]. Having said that, there is anecdotal evidence of isolated instances of hemodynamic instability or reversible vagal neuroapraxia due to positioning of the vagus electrode [38–40]. In patients with second- or third-degree atrioventricular block, no clinically relevant changes in heart rate or blood pressure, cardiac arrhythmia, or other hemodynamically important events were identified despite careful monitoring [41]. Considering experimental, animal, and human data, CVS at ≤2 Hz is reasonably safe [17,19,31,42–44], notably likewise young children [33].

Adverse EMG events, intraoperative loss of signal and trouble shooting

To facilitate interpretation of quantitative EMG signals indicative of impending RLN injury, distinct 'combined events', consisting of concordant changes in both signal amplitude (≥50% decreases) and latency (>10% increases), were defined (Figs. 2 and 3A) [17]. A proof-of-concept study of 52 patients (52 nerves at risk) showed that inappropriate traction injures the RLN. In an international multicentre study of 115 patients with persistent LOS, 80% of LOS events were caused by neural traction [45]. An institutional review of the first 101 patients monitored under CVS found that 68% (13 of 19) of combined events resolved after halting the causative surgical maneuver [40]. Another series of 102 patients found that for combined events, 73% of which were reversible, had positive and negative predictive values of 33% and 97%, respectively [19]. Isolated changes in amplitude or latency were unassociated with vocal cord paralysis. Another study of 788 patients (1314 nerves at risk) found that 80% (63 of 77) of combined events did not degrade to LOS upon release of the related maneuver to the nerve [46]. In another investigation including 455 nerves at risk, discontinuation of harmful retraction led to functional recovery of all distressed nerves, but only if LOS was yet incomplete [47].

Depending on the type and time course of nerve injury we can see varying changes in amplitude and latency. In certain slower injury scenarios such as mild ongoing traction amplitude decrease and latency increase occur together. In more acute and significant injuries EMG change can be subdivided into two successive EMG phases with amplitude depression first then latency elevation. Surgical strategy is geared at avoiding transitioning from milder injury into more serious injury which is not necessarily reversible by promptly releasing distressed nerves [3,21,24].

The International Neuromonitoring Study Group defines LOS as an amplitude decrease of <100 μV [2,45] and also distinguishes between.

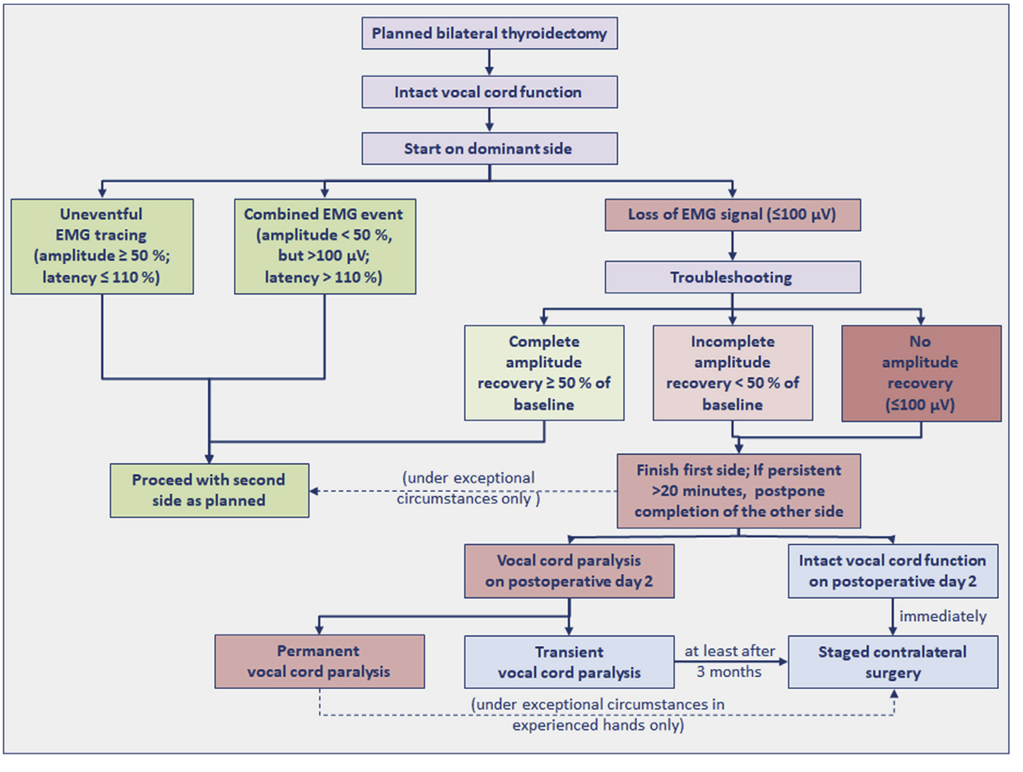

Fig. 2. Management algorithm for CVS-guided planned bilateral thyroidectomy.

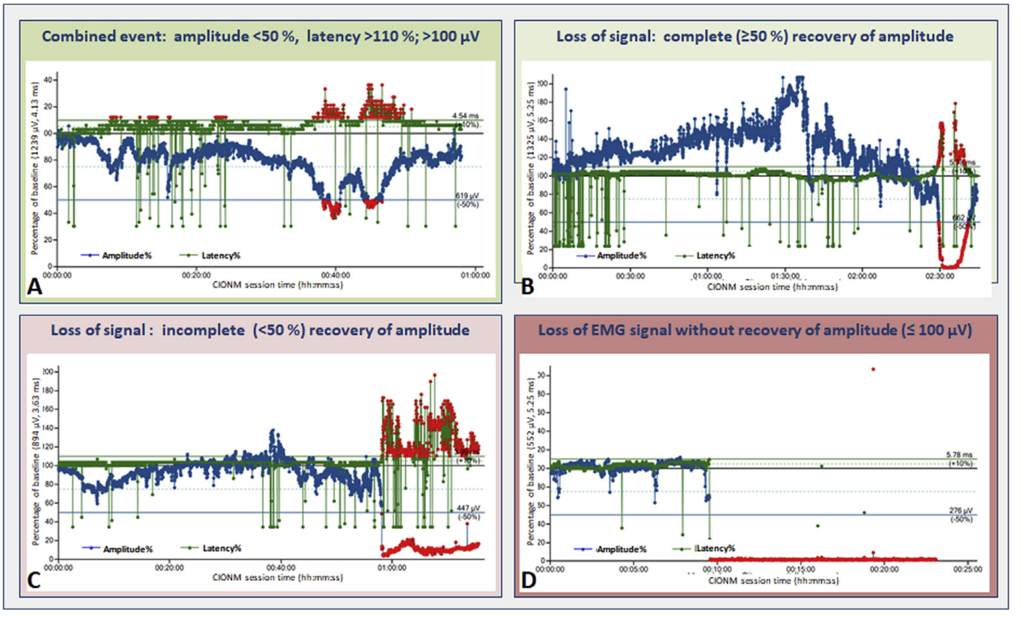

Fig. 3. Development of combined event and loss of signal with complete, incomplete and without intraoperative amplitude recovery; the blue curve denotes nerve amplitude, whereas the green curve indicates latency. A. 'Combined event', consisting of concordant changes in nerve amplitude (≥50% decreases) and latency (>10% increases), suggesting impending nerve injury, and normal postoperative vocal cord function. B. Complete intraoperative amplitude recovery (≥50% of baseline) after loss of signal with normal postoperative vocal cord function. C. Incomplete intraoperative amplitude recovery (amplitude <50% of baseline) after loss of signal with transient postoperative vocal cord palsy. D. Definitive loss of signal without intraoperative recovery and transient postoperative vocal cord paralysis.

- segmental type 1 injury, characterized by the loss of nerve function downstream of (distal to) the point of damage toward the larynx, regardless of the level of upstream (proximal) nerve stimulation, and
- global type 2 injury, associated with complete loss of function along the course of the vagus nerve and RLN

Segmental type 1 and global type 2 injuries differ greatly as to time to loss of the nerve monitoring signal and the dynamics of amplitude loss [23,45]. Unlike most segmental type 1 injuries in which the nerve monitoring signal is lost all on a sudden, global type 2 injuries are preceded by combined events, providing greater lead time before the damage becomes irreversible [17,18,23]. Because segmental LOS type 1 is infrequently preceded by graded partial EMG changes, CVS may only be able to mitigate, not prevent, segmental type 1 injuries. Nerves of small caliber, that branch outside the larynx fully dissected 360° from the surgical bed, or course in front of the inferior thyroid artery are particularly prone to injury [17,48].

Differentiation of LOS into segmental type 1 and global type 2 has significant prognostic implications. Segmental LOS type 1 entails more severe nerve damage than global LOS type 2. Definitive LOS strongly correlates with early postoperative vocal cord paralysis, affecting 95% of patients with segmental LOS type 1, as compared to 70% of patients with global LOS type 2 [45].

For optimal predictive power, strict adherence to the International Neuromonitoring Study Group's L1, V1, R1, R2, V2, L2 concept and LOS troubleshooting algorithm is mandatory [2,21]. On this premise, CVS features a sensitivity of 90.9%, specificity of 99.7%, positive predictive value of 88.2%, and negative predictive value of 99.8% [46], with a close correlation between the EMG signals and postoperative vocal cord function. Intermittent IONM, leaving unsupervised intervals between stimulation cycles and barely enabling distinction between incomplete and complete signal recovery, cannot provide a comparative level of risk reduction [49–52].

When LOS has occurred, it is important to check the CVS system for malfunction. When the laryngeal musculature is contracting ('*laryngeal twitch*') in response to vagus stimulation on both sides, but no EMG tracing is generated, a recording side issue should be suspected. In that event, the position of the endotracheal tube must be verified, and corrected accordingly. Recording side ground, interface box and monitor connections must also be checked and glottic impedance issues due to salivary pooling be excluded. When laryngeal twitch is present only on contralateral vagus nerve stimulation and is absent on ipsilateral vagus nerve stimulation, the ipsilateral RLN injury is suspected.

Transient loss of signal (complete amplitude recovery) on the first side of resection: proceed with completion surgery on the other side as planned

Nerve recovery after segmental or global LOS is underway when the amplitude is augmented beyond <100 μV. The extent of intraoperative amplitude recovery, relative to baseline, is associated with postoperative vocal cord function and time to recovery of vocal cord function [20]. Based on 18 patients with segmental LOS type 1 and 23 patients with global LOS type 2, recovery of <50% of the nerve baseline amplitude precedes early vocal cord paralysis invariably in all patients with segmental type 1 injury, and in two-thirds of patients with global type 2 injury. Intraoperative signal recovery of ≥50% of nerve baseline amplitude (Figs. 2 and 3B) portends normal postoperative vocal cord function.

A large international study of patients who developed LOS with intraoperative signal recovery, corroborated these institutional findings [23]. Intraoperative amplitude recovery of ≥50% relative to baseline accurately predicted normal early postoperative vocal cord function in all patients after transient segmental LOS type 1 or global LOS type 2. Early vocal cord function was impaired in 10 (25%) of 40 patients with temporary global LOS type 2 and in 18 (64%) of 28 patients with temporary segmental LOS type 1.

Relative and absolute amplitude recovery of 49% and 455 μV (both $P < 0.001$) after segmental LOS type 1, and 44% ($P = 0.01$) or 253 μV ($P = 0.15$) after global LOS type 2 discriminated best between normal and abnormal early postoperative vocal cord function on receiver-operating characteristic analysis [23]. Absolute amplitude thresholds did not fare better (after segmental LOS type 1) or worse (after global LOS type 2) than relative amplitude thresholds in predicting early postoperative vocal cord function. Pragmatically, it is prudent to use the amplitude threshold of ≥50% for both types of LOS. This single threshold accurately predicts normal early postoperative vocal cord function after segmental LOS type 1, but slightly underestimates normal early postoperative vocal cord function after global LOS type 2, the milder form of nerve injury. After LOS, segmental type 1 nerve injury resolves within 6.9–8.0 min; and global type 2 injury within 13.0–15.6 min. This illustrates that waiting for the nerve to regain ≥50% of its baseline is futile after 20 min [20,23,53].

Persistent loss of signal (incomplete amplitude recovery) after loss of signal on the first side of resection: postpone completion surgery on the other side

The above information is pivotal to determine whether to defer (two-stage approach), or proceed in the same session (one-stage approach) with completion surgery on the other side. When LOS persist for more than 20 min after the onset of LOS, or the nerve amplitude recoup <50% of its baseline (Figs. 2 and 3C, D), it is preferable to embark on a two-staged approach to preclude bilateral RLN paralysis [3,11]. This advice is based on the observation that 94.6% of patients with incomplete recovery of segmental LOS type 1, and 69.5% of patients with incomplete recovery of global type 2 have early postoperative vocal cord paralysis [20]. This option is recommended in bilateral benign goiter, Graves' disease, or low-risk thyroid carcinoma (differentiated or medullary thyroid carcinoma) [54].

Unless the nerve amplitude regains >50% of its baseline, completion surgery of the other side, barring rare circumstances, should not be attempted. Such rare exceptions include advanced thyroid cancers when time is critical to achieve local control, for instance through radioactive iodine therapy, radiation therapy, or targeted therapy and should be jointly discussed with the entire treating team and of course importantly the patient and their family [11,53,54].

Taking a middle ground, adoption of a ‘cautious’ surgical approach has been advocated as a potentially sound and safe alternative, at least in high-volume referral units [15]: Subtotal resection of the other side, keeping the line of resection ventral to the plane of the RLN at a distance from the RLN, balances the risk of disease recurrence with the need to stay clear of the solely functioning nerve [54]. The first component of the benefit-risk equation, the residual risk of recurrent disease arising from the thyroid remnant is unclear in the absence of long-term clinical outcome data. Also the line of resection assumes RLN positional information that is only estimated.

When the underlying thyroid condition is benign and not life-threatening, interests of patient safety always outweigh considerations of economy and convenience.

Timing of completion surgery

The time of completion surgery is first and foremost determined by the recovery of vocal cord function, which can be supported by voice therapy. A secondary consideration is the risk of surgical complications related to scar formation and adhesions in the thyroid bed obscuring surgical planes, which becomes less pronounced after the first three postoperative days and after 3 months of the first operation [55,56]. Vocal cord function recovery should be monitored by performing postoperative laryngoscopy, initially between 2 weeks and 2 months, then intermittently every 4 weeks, and completion surgery should be performed after the vocal cord has recovered. Vocal cord function recuperates to normal in >80% of patients with early postoperative vocal cord paralysis within 75 days of RLN injury [9].

Completion surgery is scheduled in >95% of patients, within 6 months of the initial surgery [54]. If the RLN injury does not recover within the first 6 months, a multidisciplinary team needs to explore available surgical and non-surgical treatment options balancing disease and patient related factors. When completion surgery is still warranted, prior fixation of the paralytic vocal cord by an Otolaryngologist Head and Neck Surgeon specialist may be useful to ensure airway patency and circumvent emergency tracheotomy in the event of contralateral RLN damage at reoperation [53].

Medicolegal considerations

Postoperative RLN paralysis is a leading course of litigation [29,57,58]. Unilateral RLN paralysis typically is regarded as an expected risk, which was disclosed and accepted by the patient upon informed consent. For bilateral RLN paralysis, the situation may be different [29,58]. Description of all operative steps in a detailed and complete operative note is an important vindicative instrument, which the plaintiff's attorneys will be scrutinizing for inconsistencies or gaps of information and documentation [59]. The prudent use of IONM, which entails printing out and filing relevant EMG tracings with the chart, may offer some protection against unfounded claims [6,30].

Cost implications of staged surgery

Recently, Al-Qurayshi et al. [60] evaluated the cost-effectiveness of neural monitoring in relation to LOS and subsequently staged thyroidectomy. They utilized a markov Chain model with monte carlo simulation cost modeling. The contralateral nerve injury was estimated conservatively at 1%. The study found that IONM with LOS incorporation into the surgical strategy, leading to staged surgery was the most cost-effective algorithm for all rates of contralateral nerve paralysis (ranging from 1 to 17%).

Conclusion

The advent of CVS, eliminating lag time between nerve dissection with potential trauma and stimulation, has transformed our thyroid surgical landscape: tailoring intraoperative decision making to determine the safest course of action for the individual patient. Continuous intraoperative nerve monitoring enables mitigation of traction-related injury to the RLN. Electromyographic precursor lesions, termed combined events, prompt surgeons to cease harmful surgical maneuvers and release the nerve before it is irreversibly damaged. Complete RLN recovery, defined as restitution of the nerve amplitude to $\geq$50% of baseline, assures the surgeon that it is safe to pursue completion surgery of the other side in one session. If this restitution is incomplete or absent (<50% of amplitude baseline), it is advisable to delay completion surgery until the nerve function has fully recovered. It is important to include these scenarios and associated surgical strategies in the preoperative discussion with the patient during the informed consent process.

Conflicts of interest

Henning Dralle was remunerated by Medtronic and Inomed for giving lectures on intraoperative nerve monitoring.

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Author contributions

(1) Conception and design: RS, AM.
(2) Administrative Support: HD.
(3) Provision of study materials or patients: RS, HD.
(4) Collection and assembly of data: RS.
(5) Data analysis and interpretation: All authors.
(6) Manuscript writing: RS, AM.
(7) Final approval of manuscript: All authors.

Practice points

- The advent of continuous vagus stimulation (CVS), eliminating lag time between nerve preparation and stimulation, has transformed the neuromonitoring landscape: tailoring intraoperative decision making to determine the safest course of action for the individual patient.
- For correct interpretation, intraoperative EMG findings must be correlated with vocal cord function. Laryngoscopy forms an integral part of the pre- and postoperative work-up for thyroid surgery.
- The informed consent needs to include details regarding the use of CVS and the potential need for a staged procedure after definitive LOS on the first side of resection.
- For optimal predictive power, the INMSG's L1, V1, R1, R2, V2, L2 concept and LOS trouble-shooting algorithm must be adhered to. On this premise, CVS reaches a sensitivity of 90.9%, specificity of 99.7%, PPV of 88.2%, and NPV of 99.8%.
- Definitive LOS strongly correlates with postoperative vocal cord paralysis, affecting 95% of patients with segmental LOS type 1 and 70% of patients with global LOS type 2.
- Complete recovery of the nerve amplitude to $\geq$50% of baseline makes it safe to pursue completion surgery of the other side in one session and occurs within 20 min of the adverse EMG events if occurring intraoperatively. If this recovery is incomplete or absent (<50% of amplitude baseline), completion surgery should be postponed.
- Description of all operative steps in a detailed and complete operative note along with documentation of EMG tracings obtained during IONM are important defense tools during a medico-legal inquiry.

Research agenda

- The lack of availability of smaller circumferential clip electrodes and tube surface electrodes hamper extension of CVS to smaller children undergoing thyroid surgery, calling for custom-fit versions of adult electrodes suitable to use in children ≤6 years.

References

[1] Riddell V. Thyroidectomy: prevention of bilateral recurrent nerve palsy. Results of identification of the nerve over 23 consecutive years (1946-69) with a description of an additional safety measure. Br J Surg 1970;57:1–11.

*[2] Randolph G, Dralle H, International Neuromonitoring Study Group. Electrophysiologic recurrent laryngeal nerve monitoring during thyroid and parathyroid surgery: international standards guideline statement. Laryngoscope 2011; 121(Suppl 1):S1–16.

[3] Schneider R, Randolph GW, Barczynski M, et al. Continuous intraoperative neural monitoring of the recurrent nerves in thyroid surgery: a quantum leap in technology. Gland Surg 2016;5:607–16.

[4] Cannizzaro MA, Lo Bianco S, Picardo MC, et al. How to avoid and to manage post-operative complications in thyroid surgery. Updates Surg 2017;69:211–5.

[5] Deniwar A, Kandil E, Randolph G. Electrophysiological neural monitoring of the laryngeal nerves in thyroid surgery: review of the current literature. Gland Surg 2015;4:368–75.

[6] Dralle H. Surgical assessment of complications after thyroid gland operations. Chirurg 2015;86:70–7.

[7] Sadowski SM, Soardo P, Leuchter I, et al. Systematic use of recurrent laryngeal nerve neuromonitoring changes the operative strategy in planned bilateral thyroidectomy. Thyroid 2013;23:329–33.

[8] Goretzki PE, Schwarz K, Brinkmann J, et al. The impact of intraoperative neuromonitoring (IONM) on surgical strategy in bilateral thyroid diseases: is it worth the effort? World J Surg 2010;34:1274–84.

*[9] Dralle H, Sekulla C, Lorenz K, et al. Loss of the nerve monitoring signal during bilateral thyroid surgery. Br J Surg 2012;99: 1089–95.

[10] Bergenfelz A, Salem AF, Jacobsson H, et al. Risk of recurrent laryngeal nerve palsy in patients undergoing thyroidectomy with and without intraoperative nerve monitoring. Br J Surg 2016;103:1828–38.

[11] Schneider R, Lorenz K, Sekulla C, et al. Surgical strategy during intended total thyroidectomy after loss of EMG signal on the first side of resection. Chirurg 2015;86:154–63.

[12] Sitges-Serra A, Fontané J, Dueñas JP, et al. Prospective study on loss of signal on the first side during neuromonitoring of the recurrent laryngeal nerve in total thyroidectomy. Br J Surg 2013;100:662–6.

[13] Khamsy L, Constanthin PE, Sadowski SM, et al. Loss of neuromonitoring signal during bilateral thyroidectomy: no systematic change in operative strategy according to a survey of the French Association of Endocrine Surgeons (AFCE). BMC Surg 2015;6:15–95.

[14] www.inmsg.org/(last accessed 12 June 2019).

[15] Sitges-Serra A, Gallego-Otaegui L, Fontané J, et al. Contralateral surgery in patients scheduled for total thyroidectomy with initial loss or absence of signal during neural monitoring. Br J Surg 2019;106:404–11.

[16] Angelos P. Ethical and medicolegal issues in neuromonitoring during thyroid and parathyroid surgery: a review of the recent literature. Curr Opin Oncol 2012;24:16–21.

*[17] Schneider R, Randolph GW, Sekulla C, et al. Continuous intraoperative vagus nerve stimulation for identification of imminent recurrent laryngeal nerve injury. Head Neck 2013;35:1591–8.

[18] Schneider R, Bures C, Lorenz K, et al. Evolution of nerve injury with unexpected EMG signal recovery in thyroid surgery using continuous intraoperative neuromonitoring. World J Surg 2013;37:364–8.

*[19] Phelan E, Schneider R, Lorenz K, et al. Continuous vagal IONM prevents RLN paralysis by revealing initial EMG changes of impending neuropraxic injury: a prospective, multicenter study. Laryngoscope 2014;124:1498–505.

*[20] Schneider R, Sekulla C, Machens A, et al. Dynamics of loss and recovery of the nerve monitoring signal during thyroidectomy predict early postoperative vocal fold function. Head Neck 2016;38:E1144–51.

[21] Schneider R, Machens A, Randolph GW, et al. Opportunities and challenges of intermittent and continuous intraoperative neural monitoring in thyroid surgery. Gland Surg 2017;6:537–45.

[22] Schneider R, Lorenz K, Machens A, et al. Continuous intraoperative neuromonitoring (CIONM) of the recurrent laryngeal nerve. In: Randolph GW, editor. The recurrent and superior laryngeal nerves. 1st ed. Springer International Switzerland; 2016. p. 169–83.

*[23] Schneider R, Randolph G, Dionigi G, et al. Prediction of postoperative vocal fold function after intraoperative recovery of loss of signal. The International Neuromonitoring Study Group's PREC Study. Laryngoscope 2019;129:525–31.

[24] Schneider R, Machens A, Randolph G, et al. Evolution and progress of continuous intraoperative neural monitoring. Ann Thyroid 2018;3:29.

[25] Lorenz K, Abuazab M, Sekulla C, et al. Results of intraoperative neuromonitoring in thyroid surgery and preoperative vocal cord paralysis. World J Surg 2014;38:582–91.

[26] Dionigi G, Donatini G, Boni L, et al. Continuous monitoring of the recurrent laryngeal nerve in thyroid surgery: a critical appraisal. Int J Surg 2013;11(Suppl 1):S44–6.

[27] Fontenot TE, Randolph GW, Setton TE, et al. Does intraoperative nerve monitoring reliably aid in staging of total thyroidectomies? Laryngoscope 2015;125:2232–5.

[28] Uldry E, Schäfer M, Saadi A, et al. Patients' preferences on information and involvement in decision making for gastrointestinal surgery. World J Surg 2013;37:2162–71.

[29] Dralle H, Lorenz K, Machens A. Verdicts on malpractice claims after thyroid surgery: emerging trends and future directions. Head Neck 2012;34:1591–6.
[30] Dralle H, Schneider R, Lorenz K, et al. Vocal cord paralysis after thyroid surgery: current medicolegal aspects of intraoperative neuromonitoring. Chirurg 2015;86:698–706.
[31] Schneider R, Przybyl J, Hermann M, et al. A new anchor electrode design for continuous neuromonitoring of the recurrent laryngeal nerve by vagal nerve stimulations. Langenbeck's Arch Surg 2009;394:903–10.
[32] Kamani D, Potenza AS, Cernea CR, et al. The non recurrent laryngeal nerve: anatomic and electrophysiologic algorithm for reliable identification. Laryngoscope 2015;125:503–8.
[33] Schneider R, Machens A, Sekulla C, et al. Twenty-year experience of paediatric thyroid surgery using intraoperative nerve monitoring. Br J Surg 2018;105:996–1005.
[34] Ulmer C, Koch K, Seimer A, et al. Real-time monitoring of the recurrent laryngeal nerve: an observational clinical trial. Surgery 2008;143:359–65.
[35] Dionigi G, Chiang FY, Dralle H, et al. Safety of neural monitoring in thyroid surgery. Int J Surg 2013;11(Suppl 1):S120–6.
[36] Angeletti F, Musholt PB, Musholt TJ. Continuous intraoperative neuromonitoring in thyroid surgery. Surg Technol Int 2015;27:79–85.
[37] Lörincz BB, Möckelmann N, Busch CJ, et al. Automatic periodic stimulation of the vagus nerve during single-incision transaxillary robotic thyroidectomy: feasibility, safety, and first cases. Head Neck 2016;38:482–5.
[38] Terris DJ, Chaung K, Duke WS. Continuous vagal nerve monitoring is dangerous and should not routinely be done during thyroid surgery. World J Surg 2015;39:2471–6.
[39] Brauckhoff K, Vik R, Sandvik L, et al. Impact of EMG changes in continuous vagal nerve monitoring in high-risk endocrine neck surgery. World J Surg 2016;40:672–780.
*[40] Marin Arteaga A, Peloni G, Leuchter I, et al. Modification of the surgical strategy for the dissection of the recurrent laryngeal nerve using continuous intraoperative nerve monitoring. World J Surg 2018;42:444–50.
[41] Schneider R, Machens A, Bucher M, et al. Continuous intraoperative monitoring of vagus and recurrent laryngeal nerve function in patients with advanced atrioventricular block. Langenbeck's Arch Surg 2016;401:551–6.
[42] Van Slycke S, Gillardin JP, Brusselaers N, et al. Initial experience with S-shaped electrode for continuous vagal nerve stimulation in thyroid surgery. Langenbeck's Arch Surg 2013;398:717–22.
[43] Mangano A, Kim HY, Wu CW, et al. Continuous intraoperative neuromonitoring in thyroid surgery: safety analysis of 400 consecutive electrode probe placements with standardized procedures. Head Neck 2016;38(Suppl 1):E1568–74.
[44] Xiaoli L, Wu CW, Kim HY, et al. Gastric acid secretion and gastrin release during continuous vagal neuromonitoring in thyroid surgery. Langenbeck's Arch Surg 2017;402:265–72.
*[45] Schneider R, Randolph G, Dionigi G, et al. Prospective study of vocal fold function after loss of the neuromonitoring signal in thyroid surgery: the International Neural Monitoring Study Group's POLT Study. Laryngoscope 2016;126:1260–6.
*[46] Schneider R, Sekulla C, Machens A, et al. Postoperative vocal fold palsy in patients undergoing thyroid surgery with continuous or intermittent nerve monitoring. Br J Surg 2015;102:1380–7.
[47] Kandil E, Mohsin K, Murcy MA, et al. Continuous vagal monitoring value in prevention of vocal cord paralysis following thyroid surgery. Laryngoscope 2018;128:2429–32.
[48] Wu CW, Wang MH, Chen CC, et al. Loss of signal in recurrent nerve neuromonitoring: causes and management. Gland Surg 2015;4:19–26.
[49] Henry BM, Graves MJ, Vikse J, et al. The current state of intermittent intraoperative neural monitoring for prevention of recurrent laryngeal nerve injury during thyroidectomy: a PRISMA-compliant systematic review of overlapping meta-analyses. Langenbeck's Arch Surg 2017;402:663–73.
[50] Yang S, Zhou L, Lu Z, et al. Systematic review with meta-analysis of intraoperative neuromonitoring during thyroidectomy. Int J Surg 2017;39:104–13.
[51] Malik R, Linos D. Intraoperative neuromonitoring in thyroid surgery: a systematic review. World J Surg 2016;40:2051–8.
[52] Pisanu A, Porceddu G, Podda M, et al. Systematic review with meta-analysis of studies comparing intraoperative neuromonitoring of recurrent laryngeal nerves versus visualization alone during thyroidectomy. J Surg Res 2014;188:152–61.
*[53] Schneider R, Randolph GW, Dionigi G, et al. International neural monitoring study group guideline 2018 part I: staging bilateral thyroid surgery with monitoring loss of signal. Laryngoscope 2018;128(Suppl 3):S1–17.
[54] Wu CW, Sun H, Zhang G, et al. Staged thyroidectomy: a single institution perspective. Laryngoscope Investig Otolaryngol 2018;3:326–32.
[55] Erbil Y, Bozbora A, Ademoglu E, et al. Is timing important in thyroid reoperation? J Otolaryngol Head Neck Surg 2008;37:56–64.
[56] Glockzin G, Hornung M, Kienle K, et al. Completion thyroidectomy: effect of timing on clinical complications and oncologic outcome in patients with differentiated thyroid cancer. World J Surg 2012;36:1168–73.
[57] Shaw GY, Pierce E. Malpractice litigation involving iatrogenic surgical vocal fold paralysis: a closed-claims review with recommendations for prevention and management. Ann Otol Rhinol Laryngol 2009;118:6–12.
[58] Abadin SS, Kaplan EL, Angelos P. Malpractice litigation after thyroid surgery: the role of recurrent laryngeal nerve injuries, 1989–2009. Surgery 2010;148:718–22.
[59] Verzeletti A, Vassalini M, Bin P, et al. Malpractice claims related to recurrent laryngeal nerve injury: forensic remarks regarding 15 cases. Egypt J Food Sci 2016;6:501–4.
[60] Al-Qurayshi Z, Kandil E, Randolph GW. Cost-effectiveness of intraoperative nerve monitoring in avoidance of bilateral recurrent laryngeal nerve injury in patients undergoing total thyroidectomy. Br J Surg 2017;104:1523–31.