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Evolution of Intra-operative Nerve Monitoring as a Revolution in Thyroid Surgery: A PRISMA Compliant Systematic Review

Haleema Sadia, Hira Ashraf, Talat Waseem

INTRODUCTION In the past two decades, intra-operative nerve monitoring (IONM) has turned into a powerful risk minimisation tool. The importance and superiority of IONM over visual identification of RLN during thyroidectomy in the absence of IONM, has not been completely justified in meta-analysis and articles related to this topic. Continuous IONM (C-IONM) is superior to intermittent IONM (I-IONM) due to its real time electromyographic tracings intra-operatively and thus reducing the RLN palsy, in turn decreases vocal cord paralysis post-operatively. C-IONM urges surgeons to reverse the harmful surgical manoeuvres to avoid the permanent traction related nerve injury; it also plays an important part in the surgical concept of staged thyroidectomy.

OBJECTIVEof this review article is to shed some light on IONM technique, discuss its pros and cons and detailed review of its two types and how it is taking the neck surgery by storm, how it's equipping young surgeons with confidence by honing their surgical skills.

METHODSThis review article is written according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses abbreviated as PRISMA guidelines. Literature search was done through Google Scholar, PubMed and ERIC. Search terms were: "intra-operative neuromonitoring" AND "continuous intro-operative nerve monitoring" or "intermittent intra-operative nerve monitoring" AND "recurrent laryngeal nerve" or "RLN" AND "thyroid gland" or "thyroidectomy". 397 articles were identified out of which 41 articles were reviewed at length and were used for identification of themes.

RESULTSIn recent years, the volume of thyroid procedures are expanding so did risk minimization measures protecting RLN, although the incidence of injury to RLN is low in experienced hands, it may diminish the patient's quality of life resulting in permanent post-operative compromise of voice quality and that in turn can result litigation for malpractice for the surgeon responsible. IONM especially C-IONM helps decreasing the incidence of imminent RLN palsy by providing the real-time neuromonitoring intra-operatively also helps in perfecting the surgical skills of young surgeons. Proper documentation of IONM helps in case of litigation as well.

CONCLUSIONThis review article concludes that IONM could greatly decrease the incidence of RLN injury, total, transient and permanent injury, as compared to conventional visual identification of RLN. IONM has proved itself useful in timely predicting the post-operative vocal cord palsy intra-operatively by signaling the impending nerve injury early on. This enables surgeons to withdraw surgical maneovers causing the nerve injury and in turn hone their surgical skills.

KEYWORDS Intra-operative nerve monitoring (IONM), recurrent laryngeal nerve (RLN), recurrent laryngeal nerve palsy, thyroidectomy, continuous IONM (c-IONM), intermittent IONM (I-IONM).
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A case of total thyroidectomy was planned for papillary carcinoma of thyroid under the guidance of IONM in the Department of Surgery, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey. Surgeons started their dissection from right lobe of thyroid gland containing the malignant solid nodule. Sound signals were obtained after stimulation of vagus nerve and recurrent laryngeal nerve (RLN) before dissection while recording the wave amplitude. Right RLN was completely exposed and isolated during dissection. After dissection of the nodule, anatomically intact RLN was stimulated and showed the loss of signal (LOS) without recordable amplitude. Stimulation of vagus nerve confirmed the LOS, indicating post dissection permanent or transient injury to the nerve. Due to LOS after right hemi-thyroidectomy further resection of left lobe was halted and patient was closed. Electrophysiological monitoring of the right RLN showed a segmental (type1) injury. Post-operative laryngoscopy was done and it confirmed right unilateral vocal cord (VC) palsy. The diagnosis on the basis of pathological report was papillary thyroid cancer of the right lobe. The right vocal cord normal function was recovered in third post op month. Completion left lobectomy was performed after 4 months of the primary surgery, as a delayed procedure with IONM as well. Laryngoscopy done post-operatively confirmed the normal function of both vocal cords.[1] Timely identification of LOS of anatomically intact RLN intra-operatively and delaying the left lobectomy on that basis, with the use of IONM technique, saved bilateral vocal cord palsy (VCP) in this papillary thyroid carcinoma patient.

Recurrent laryngeal nerve palsy (RLNP) is a very common and feared complication of thyroid and parathyroid surgery. However, RLNP rates have markedly decreased due to routine visual identification of the RLN[2],[3]. Unilateral RLNP causes hoarseness of voice and that in turn affect the quality of life of the patient massively. Fortunately, this impairment is short-lived in most cases, in contrast to bilateral RLNP which mostly causes permanent kind of hoarseness[4,5]. The gold standard has always been the visual identification of RLN before dissecting into the thyroid gland itself.

One of the products of technology in surgical domain is intra-operative nerve monitoring during thyroid surgery (IONM). After its invention there is a continuous debate whether it significantly reduces the RLNP rates or not. Also, there is an open debate front regarding intermittent IONM (I-IONM) and continuous IONM(C-IONM). According to recent literature on the use of I-IONM, there was no significant reduction in RLNP rates with I-IONM[6]. Also according to some, the main advantage of I-IONM is the prevention of bilateral RLNP with the implementation of two staged thyroidectomy[7].

Continuous intra-operativenerve monitoring (C-IONM) is rather latest technique and it potentially enables the surgeon to react before irreversible damage to the RLN occurs[8,9]. An electrode is applied on the vagus nerve in C-IONM during the entire operation to measure the electromyographic activity of the muscles innervated by the RLN. Commonly, injury to the RLN or injury to any nerve intra-operatively, occur mostly due to thermal injury or traction followed by clamping, as shown in a multi-centre study of 115 cases with loss of signal (LOS) caused by traction to RLN in 80% of the cases[10]. All kind of injuries cannot be prevented by IONM hence the difference between each type of injury is critical when it comes to C-IONM. If tension or traction is released when detected early by IONM, injuries can be avoided and potentially reversible. This has been shown by Phelan[8]and Schneider et al. [9] that more than 73% and 82% of events, respectively, were reversible during surgery when prompt corrective measures were applied. C-IONM offers higher sensitivity for early and prompt detection of RLNP incidence upon comparing RLNP rates between the two techniques I-IONM and C-IONM [9]. Furthermore, electrode positioning was reported to be safe during C-IONM in an analysis of 400 vagal nerve dissections [11]. On the contrary, Terris et al. [12]reports two cases of LOS, one due to hypotension and bradycardia after the vagal electrode was used, and the second case was, vagal nerve injury resulting in temporary RNLP due to ecletrode application, concluding this to be a harmful and invasive technique. Another group, Katrin et al., studying high-risk neck surgeries reports one case of loss of signal which was caused by vagal electrode and multiple situations of EMG artefacts[13].To sum it all up, C-IONM is superior in affectivity over I-IONM in prevention of RLNP [14]. In 2012, C-IONM was introduced in Geneva for selective use in complicated surgeries for example invasive thyroid cancer, retro-sternal goitre, Grave's disease and re-intervention surgeries.

METHODS

This review article is written according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses abbreviated as PRISMA guidelines with the objective to analyse data available for IONM in thyroid surgery.

Search Strategy and Data Extraction:

Narrative approach was used to review the literature in order to perform comprehensive, critical and objective analysis of the available data. A comprehensive literature search was done via the databases PubMed, ERIC, Google Scholar and Sci-Hub from 1996-2020. Relevant articles were added manually as well by going through the references. Search terms used in search engines were: "intra-operative nerve monitoring" AND "continuous intra-operative nerve monitoring" OR "intermittent intra-operative nerve monitoring" AND "recurrent laryngeal nerve" OR "RLN" AND "thyroid gland" OR "thyroidectomy". All search papers were reviewed according to the selected search strategy.

Selection Criteria and Quality Assessment:

433 articles were identified using the computer literature search of PubMed and Google scholar. Titles and abstracts of all the papers were reviewed using the inclusion and exclusion criteria. 32 articles were excluded for duplication, remaining 401 articles were viewed and 41 articles related to the topic were included in this literature review. 103 full-text articles were assessed for eligibility and 62 articles were excluded on the basis of exclusion criteria. No language, age or gender restrictions were applied. All papers from 1996 to 2021 were included. Exclusion criteria included duplicate articles, poster presentations, articles not related to the topic, articles on minimally invasive video thyroidectomy, articles on endoscopic thyroidectomy, papers on paediatric thyroidectomy and articles on robot assisted thyroidectomy. The article selection process is given in Diagram 1.

Data Extraction and Detailed Analysis:

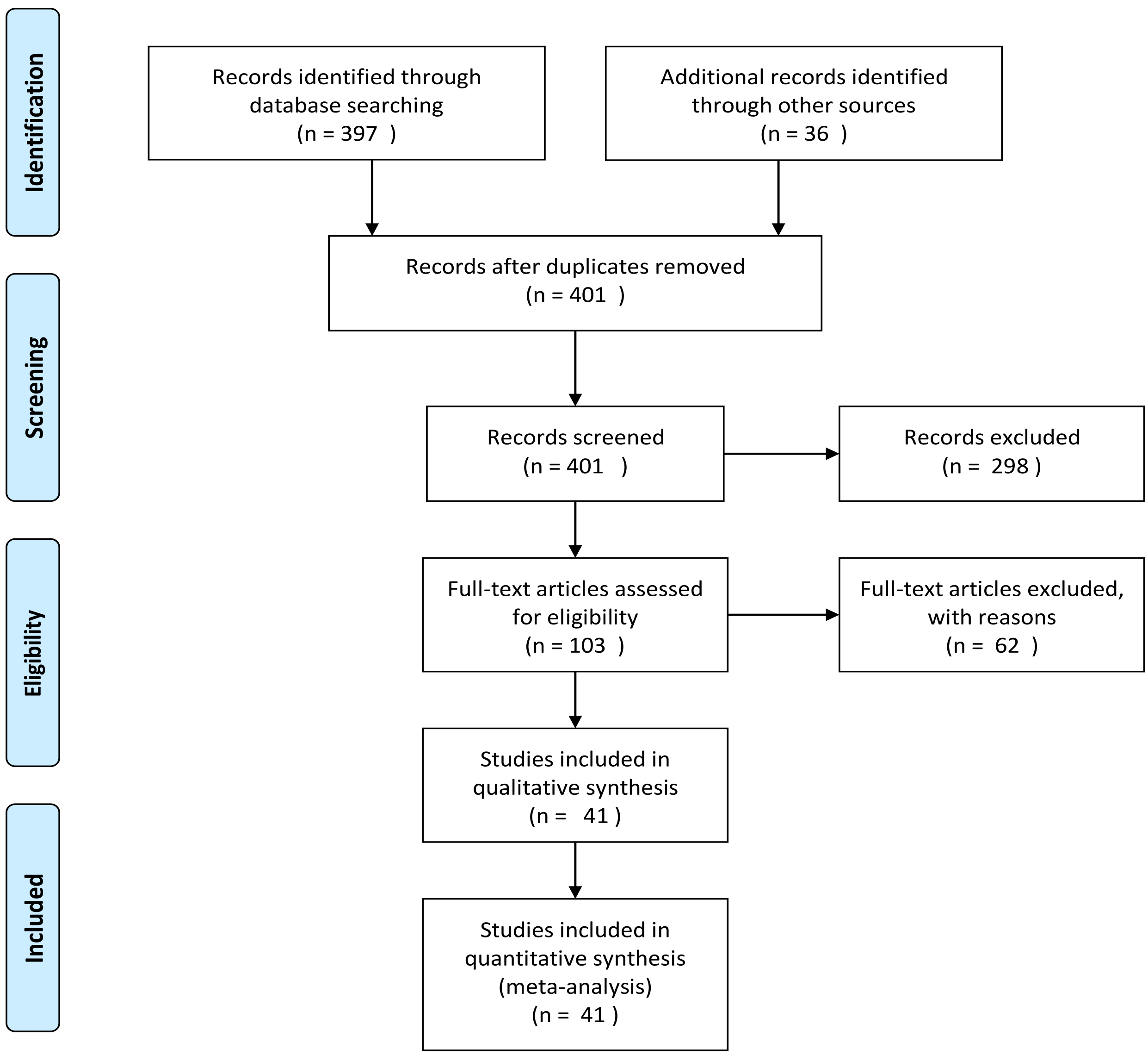
Thematic analysis of each paper was done. Information about year of publication, name of the author, country of origin, methods of study and themes identified were collected and coded. The themes identified through analysis of the data are given in table 1.

RESULTS

433 articles were identified through comprehensive computer literature search. 41 articles were included after the screening process after removing duplicate articles. Some recurrent themes were identified after detailed analysis of the selected papers which are described in Table1.

Figure 1: PRISMA Flowchart- Article selection process through computer literature search and analysis:

PRISMA 2009 Flow Diagram



Year	Author	Country	Research Method	Themes Identified
1996	Lamade (Lamade et al., 1996)	Germany	Initial Wet Lab Technique development	IONM system for RLN is reliable and easy to use, even the imminent injury to RLN can be demonstrated by signal changes.
1996	DavidW. Eisele(DW Eisele,1996)	USA	42 RLN were monitored in 31 patients by direct RLN stimulation with electrodes on ETT at the level of true vocal cords	NIM-2 EMG ETT is a safe, effective and simplified method for RLN monitoring during thyroidectomy or parathyroidectomy
2005	Dionigi (Dionigi et al., 2005)	Italy	Review article on the influence of new technology on thyroid surgery including IONM	RLN monitoring and stimulation may be a useful technique when identification of RLNis expected to be difficult (redo surgery) also specific training is required for this new device.
2007	Shindo (Shindo, Chheda, 2007)	USA	Retrospective study of 684 patients (1043 nerves at risk) who underwent thyroidectomy under GA	Monitoring of the RLN does not appear to reduce the incidence of post-operative vocal cord paralysis
2007	Lamadé (Lamadé et al., 2007)	Germany	Original article discusses c-IONM of RLN with a new vagal electrode	Continuous RLN monitoring by stimulation of the vagal nerve is feasible, safe, easy to handle andcompatible with all thyroid operations technique
2008	Dionigi (Dionigi et al., 2008)	Italy	A review article	Prevention of post-operative complications, such as laryngeal nerve paralysis with IONM
2009	Schneider (Schneider et al., 2009)	Germany & Austria	An original article about c-IONM of RLN by vagal nerve stimulation	The vagal anchor electrode is safe to use and allows c-IONM without any threats, this new technique will provide more security.
2010	Jonas (Jonas et al., 2010)	Germany	Original paper, in 100 patients thyroid resection was performed using vagus electrode for continuous stimulation	Parameters e.g. signal amplitude, latency and stimulation threshold cannot be reliable warning criteria, LOS remains the most important criteria for the surgeon and this gives surgeon the possibility to react immediately.
2010	Dionigi (Dionigi et al., 2010)	Italy	Opinion paper on monitoring of RLN in thyroid surgery	New technologies have been applied in thyroid surgery, this is a transition period from the era of visualisation to era of neurophysiology of RLN
2011	Lee (Lee & Stack, 2011)	USA	Review article on intraoperative neuromonitoring during thyroidectomy	IONM Still needs to improve, there is a strong argument for its use as a teaching and research tool, residents and less-experienced thyroid surgeons may benefit from its use.
2012	Angelos (Peter Angelos, 2012)	USA	Literature review of ethical and medicolegal issues in neuromonitoring during thyroid surgery	Neuromonitoring can provide valuable information to surgeons about the functioning of RLN, but should not overestimate the benefits when discussing the technology with patients.
2012	Barczyński (Barczyński et al., 2012)	Poland	Randomized controlled trial of 210 patients for visual inspection vs neuromonitoring	Use of IONMsignificantly improved the identification rate of the nerve, as well as reduced the risk of post-operative phonation changes following thyroidectomy.
2012	Friedrich (Friedrich et al., 2012)	Germany	Prospective controlled study of 40 patients scheduled for thyroid or parathyroid surgery	C-IONM via vagal nerve stimulation appears to be safe and effective
2012	Refoyo (José Luis Pardal-Refoyo, 2012)	Spain	An original article of 259 RLNs at risk during thyroidectomy with neuromonitoring (group A: 129nerves) and without neuromonitoring (control group B: 130nerves)	Neuromonitoring helps to identify RLN and increases the security of the surgeon in the technique. It is advisable to perform neuro monitoring routinely in thyroid surgery.
2013	Schneider (Schneider et al., 2013)	Germany	Original article of 52 patients whounderwent C-IONM for thyroid surgery via vagus nerve stimulation	C-IONMReliablysignaled impendingRLN injury, enabling immediate corrective action.
2013	Dionigi (Dionigi et al., 2013)	Italy	A PubMed indexed literature review of the limitations of I-IONM and commentary about C-IONM.	C-IONM by vagal nerve stimulation enhance the standardisation process, intra-operative information of RLN, documentation, protection, training and research in modern thyroid surgery.
2013	Sadowski (Sadowski et al., 2013)	Switzerland	An original article discussing; bilateral thyroidectomy was delayed after LOS of unilateral lobectomy.	The systematic use of IONM and the change in operating strategy will lead to an almost 0% rate of bilateral recurrent laryngeal nerve palsy
2014	Barczyński (Barczyński et al., 2014)	Poland	A retrospective cohort study of 854 patients having re-operations of thyroid,now with IONM	IONM decreased the incidence of transient RLN paresis in repeat thyroid operations compared with nerve visualisation alone.
2014	Phelan (Phelan et al., 2014)	USA	Prospective multicenter tertiary study	C-IONM is safe and provides real-time RLN evaluation during surgical manoeuvres
2015	Schneider (Schneider et al., 2015)	Germany	An original article comparing C-IONM and I-IONM	Operation with C-IONM resulted in fewer permanent vocal fold plasies compared with I-IONM after thyroid surgery in patients with benign disease

2015	Deniwar (Deniwar, Kandil& Randolph, 2015)	USA	A literature review	C-IONM prevent nerve injury by detecting EMG waveform change indicating impending nerve injury.
2015	Angeletti (Angeletti, B. Musholt, J. Musholt, 2015)	Germany	An original article discussing c-IONM	C-IONM potentially enables the surgeon to react before irreversible damage to the RLN occurs.
2016	Schneider (Schneider et al., 2016)	Germany	A review article	C-IONM facilitate for early corrective action before permanent damage to the RLN has been done.
2016	Refoyo (Refoyo&Sangrador, 2016)	Spain	Systematic review of 40 articles and 54 case studies (without NM, 25; with NM, 29) with 30,922 patients	The risk of bilateral paralysis is lower in studies with neuromonitoring
2016	Schneider (Schneider et al., 2016)	Germany &USA	An original article	C-IONM can prompt corrective actions before LOS occurs, C-IONM provide better nerve protection than I-IONM, permanent RLN plasy rates are 0% with c-IONM vs. 0.4% with I-IONM
2017	Schneider (Schneider et al. 2017)	Germany	Review article	Review summarises the current key achievements of IONM; outlines opportunities for improvement regarding clinical implementation and suggests areas of future researchin this rapidly evolving field.
2017	Qurayshi (Qurayshi, Kandil& Randolph, 2017)	USA	A Markov chain model was constructed based on IONM use	Use of IONM is cost effective in patients undergoing bilateral thyroid surgery
2017	Randolph (Randolph &Kamani)	USA	Retrospective study of electrophysiologic response of 1381 RLNs	IONM of the RLN can aid in the nerve mapping, nerve identification and prognostication of post-operative vocal cord function, which can influence the surgeon's decision to proceed to bilateral surgery
2017	Christoforides (Christoforides et al., 2017)	Greece	A retrospective cohort study	Staged thyroidectomy seems very promising procedure for both patient and surgeon since it nearly eliminates one of the most fearful complications in thyroid surgery, RLN palsy
2017	Mannelli (Mannelli et al., 2017)	UK	Research article	IONM with automated periodic stimulation (APS) technical and practical steps, encourage surgeons to widen their skills and gain knowledge about its potential use
2018	Bai (Bai& Chen, 2018)	China	Literature review article	Literature search indicated that IONM could reduce the incidence of total, transient and permanent RLN injury compared with conventional visual identification
2018	Arteaga (Arteaga et al., 2018)	Switzerland	Retrospective study	C-IONM provides real-time evaluation of the RLN function, allowing for adaptation of surgical maneuvers to prevent RLNP
2018	Basarrate (Basarrate et al., 2018)	Spain	A prospective cohort study,248 consecutive thyroidectomies were included	Continuous vagal nerve monitoring is safe and allows us to assess nerve function intraoperatively
2018	Singer (Michael C. Singer, 2018)	USA	50 patients scheduled to undergo thyroidectomy were enrolled, a lead designed for CIONM was placed on the nerve	This study demonstrates the apparent safety and viability of a CIONM technique using a lead placed directly on the RLN, widespread adoption of CIONM during thyroidectomy may reduce RLN injuries.
2019	Yu (Yu et al., 2019)	China	A total of 344 patients who underwent high-risk thyroid surgery, with 238 patients operated with I-IONM and 106 patients operated with C-IONM.	Both I-IONM and C-IONM are equally safe and effective in high-risk thyroid surgery. C-IONM can help predict impending recurrent laryngeal nerve injury in real time,thereby minimizing critical maneuvers in high-risk thyroid surgery.
2019	Gürleyik (EminGürleyik, GünayGürleyik, 2019)	Turkey	Case study	IONM establishes the outcome of the neural palsy, affects the surgical decision-making, and prevents the risk of bilateral palsy.
2020	Schneider (Schneider et al., 2020)	Germany	Literature review	Review summarizes the advances of continuous IONM technology that caused a quantum leap in risk minimization for thyroid surgery, shifting current paradigms.
2020	Kim (Kim et al., 2020)	USA	An original article	Nationally, IONM is used in nearly two thirds of thyroid surgeries. IONM is associated with a lower risk of RLN palsy.
2020	Kartal (Kartal et al., 2020)	Turkey	Clinical study	Intraoperative neuromonitoring may decrease the incidence of total VCP and prevent the development of bilateral VCP, which has unfavorable results for both patients and health-care professionals.
2021	Sinclair (Sinclair et al., 2021)	USA	Observational case-control study	CIONM significantly decreased rates of postoperative transient VF paralysis and paresis over intermittent IONM alone.
2021	Abdelhamid (Abdelhamid, Aspinall, 2021)	UK	An original article	Use of IONM is associated with a decreased risk of RLN injury in thyroidectomy.

In recent years, the volume of thyroid procedures has expanded and so did risk minimization measures to protect RLN. In experienced hands, the rate of RLN palsy is low. RLNP results in permanent post-operative compromise of voice quality that may significantly affect patient's quality of life and can open a law suit for the surgeon[15]. IONM includes three steps of nerve monitoring: pre-operative, intra-operative and post-operative monitoring of RLN function.These three levels of monitoring add another dimension to thyroid surgery[16]. The prerequisites are advanced surgical skills, dissection and isolation of the RLNfollowing its visual identification.

Evolution of IONM:

- Intermittent IONM done with handheld mono-polar probes which stimulate the RLN, and needle electrodes inserted into the vocal muscle through cricothyroid membrane and through this system electrophysiological response signal is recorded.
- Intermittent IONM with handheld mono-polar probes which stimulate RLN, and surface electrodes fixed on the endotracheal tube (ETT), record the electrophysiological response signal.
- c-IONM is performed with a clip electrode attached on vagus nerve and surface electrodes fixed to the ETT to record the electrophysiological response signal intra-operatively.

c-IONM advances have produced a quantum leap in risk minimization of thyroid surgery. In some countries c-IONM is considered a standard of care in thyroid surgery patients and has gained popularity on the basis of decreased RLNP rates. Although, the cost effectiveness of this technology will remain controversial in resource-conscious environments until it becomes gold standard in the world of thyroid surgery[17].

Meta-analysis and systematic reviews on IONM:

There are multiple systematic reviews and meta-analysis which compares IONM against visual identification of RLN in the absence of IONM[17–26]. Astonishingly, many of these reviews contradict each other. There's evidence suggesting that IONM decreases both permanent and transient RLN injury rate[18,26], only transient RLN injury rate[17,25], or only permanent RLN injury rate [24]. On the contrary, other researchers did not find substantial data that proves reduction of permanent RLN injury rate [19] or reduction of both transient and permanent RLN injuries[21–23]. These contradictory results are best explained by the stepwise evolution of IONM technology from intermittent IONM to c-IONM as mentioned in detail in the previous heading and recognition of the importance of this technique and its standardisation based on the principles laid down by the International Neural Monitoring Study Group[27]. According to Schneider et al. IONM especially c-IONM is shifting current paradigms[28].

Intermittent and continuous IONM use among surgeons:

A survey by German Society of Endocrine Surgeons abbreviated as GAEK performed on 12,888 patients with benign goitre and 18,793 nerves at risk, concluded that IONM was used in 98.4% of patients and I-IONM (82.6%) was used more often than C-IONM (17.4%)[29]. A 2012 survey of German surgical units concluded that IONM was employed in 91% of thyroidectomies[30].

In 2016 survey of Surgeons of the American Head and Neck Society, 95% of surgeons said that they either used IONM routinely (60%) or selectively (35%). The most common reason for using IONM was improved surgeon confidence (55%) and increased patient's safety (54%)[31]. A survey conducted in 2019, among 1015 surgeons reported 83% of surgeons employing IONM for some or all of their operations[32]. Acceptance and usage rate of IONM is greater among younger surgeons. IONM uptake is unrelated to surgical volume, type of practice or fellowship training.

Honing surgical skills with the help of IONM by continuous feedback on nerve function:

Continuous electrophysiological feedback on the functional integrity of a nerve makes the surgical team to effectively withdraw any harmful maneuvering in turn significantly decreases the RLNP rates and also they can perfect their surgical skills[15]. This reassurance during surgery is most likely to decrease stress of the surgical team [34]. Introducing IONM routinely in thyroid surgery may also help young and less experienced surgeons to perform operations with more safety and comfort[35–37]. That can result in complication rates comparable to an experienced surgeon[38].

Documentation of and informed consent for IONM in case of Litigation:

Ethical considerations are involved in the use of reasonable risk minimization strategies [39]. In the event of litigation informed consent, containing all the strengths and weaknesses of IONM technique and in case of LOS the need to halter the surgery of the opposite side of thyroid gland to avoid bilateral vocal cord palsy, may serve as a line of defence[40].

A 2012 study, based on a 15-year period in Germany, by Dralle et al. showed 75 lawsuits of which 60% were due to RLN palsies, half of which were bilateral[41]. Gartland et al.

[42]supported these findings and found that bilateral RLNP was prediction of plaintiff verdicts, accounting for up to 18% of 128 malpractice suits in the US.These verdicts highlight the importance of properly documenting and implementing the use of risk minimisation strategies. Normal vagus nerve and RLN electrophysiological documentation pre and post dissection of the thyroid lobe provides a strong line of defence.

IONM superiority in thyroid surgery:

There are two types of LOS, type 1 is segmental LOS and type 2 is diffused LOS. Both I-IONM and c-IONM can differentiate between the two types. Whereas, c-IONM offers added benefits in minimisation of injury caused by traction, thermal injury, real-time RLN functional monitoring and EMG signal documentation. Both types of IONM suggest informed treatment plan to surgeons intra-operatively and provide strategic direction if staged thyroidectomy is required after definitive LOS on the first side of operation[15]. According to Australian College of Surgeons[43] and the German Association of Endocrine Surgeons [44] IONM has turned into a standard of care in some countries[45]. C-IONM provides real time intra-operative registration and documentation of nerve signals, it has been demonstrated that instant release of a distressed nerve decreases RLN injury chances.

Prediction of Post-operative vocal cord functions Intra-operatively:

The prediction of post-operative vocal cord palsy with the help of IONM is characterised by two scales:

- Sensitivity; 63-91% for I-IONM and 91-100% for c-IONM
- Specificity; 97-99% for I-IONM and 90-99.7% for c-IONM

In case of laryngeal nerve palsy the positive predictive value (PPV) is bound to be lower than the negative predictive value (NPV):

- PPV 38-80% for I-IONM and 48-88% for c-IONM
- NPV 97-99.8% for I-IONM and 99-100% for c-IONM

Post-operative vocal cord palsy rates are significantly lower with this technique

- Early palsy rates; 0.8-10% for I-IONM and 2.6-2.9% for c-IONM
- Permanent palsy rates; 0.2-1.5% for I-IONM and 0-1.5% for c-IONM[28].

The main difference between c-IONM and I-IONM is continuous and real time monitoring of functional integrity of RLN by c-IONM along the entire vagus-RLN pathway for detection and timely prevention of traction related injury of RLN [33,46,47]. In experienced hands c-I0NM can decrease permanent VCP rate to 0% as compared to 0.4% with I-IONM[9]. For accurate results it is important to get nerve amplitudes of greater than or equal to 500 microvolts at baseline with stimulation current of 1mA[46].

Mobilisation and resection of thyroid with greater flexibility:
C-IONM is a powerful technique which enables instant recognition of RLN injury. A multi-centre study for 115 nerves with LOS, concluded that 83% of RLN injuries were traction related, 60% among those happened near or at the ligament of Berry[10]. Findings of this multi-center study highlighted the importance of IONM-assisted thyroid mobilisation and resection. Injuries occurring due to traction are preceded by “combined events” which result in changes in the amplitude and latency relative to baseline reading. If no action is taken injury to the nerves may lead to LOS, which can be a serious and irreversible condition[8,46,47]. When these changes in amplitude and latency happen, surgeon should relax hold on the thyroid gland thus releasing tension on RLN until baseline amplitude of the nerve has regained. If change is baseline amplitude occur more than once it may be more advisable to take a median route to thyroid hilum instead of continuing a risky dissection.

C-I0NM can show its true importance when the operating field is scarred and surgical layers are annihilated such as during mobilisation of thyroid, dissection of thyroid capsule, or digital mobilisation of retrosternal thyroid. In these circumstances, it is often unfeasible to identify and map the involved nerves. A stimulating electrode attached on the vagus nerve is activated and the surgeon is constantly alerted of injury to a nerve that remains invisible[48].

Intra-operative amplitude recovery for restoring post-operative vocal cord function:
After loss of signal, segmental injury (type 1) usually resolves within 7-8 minutes and global injury (type 2) resolves within 13-15.6 minutes. This observation shows the ineffectiveness of waiting more than 20 minutes for the RLN nerve to re-gain half of its baseline amplitude [47,49]. Almost 50% of amplitude recovery predicts normal post-operative VC function in all patients after segmental or global injury. Vocal cord function is impaired upon examination post-operatively in 25% of patients with a temporary Type2 injury and 64% of patients with temporary type1 injury[49]

Staged Thyroidectomy vs same-session thyroidectomy:
When on the first side of resection loss of signal is detected and traction on the RLN nerve is stopped at once, standard procedure is to give the nerve around 20 minutes to recover 50% of its baseline amplitude. If it fails to do so, there is 85% risk of early post-operative VCP[47]. In such cases it is absolute necessity to postpone thyroidectomy (lobectomy) of the

unaffected side for at least three months to avoid bilateral VCP until VC function has fully recovered[30,50]. Contralateral surgery should only be pursued under exceptional circumstances such as advanced cancer[51]and only at hospitals which have experienced surgeons for complex neck surgeries.

Cost effectiveness of IONM:

Practice and adoption of this technique varies by geographic region and country, cost varies from $5000 to $40,000 for the equipment and from $72 to $5000 for disposables per application (recording surface tubes and vagus electrodes). In addition, indirect cost includes Glidescope video laryngoscope required for correct positioning of the recording electrodes, or ancillary staff in the operating theatre to aid in monitoring RLN function[28]. The utilisation of IONM may amount to 5 to 7% of the total thyroidectomy inpatient expense [52].

DISCUSSION

RLN injury resulting in RLNP is one of the most serious and major complications of thyroid surgery. It greatly affects patient's quality of life post-operatively. RLN injury rate is recorded to range from 0.5-10% [53]. Most surgeons believe that routine exposure and separation of RLN can protect anatomical integrity of the nerve and reduce its rate of injury[23]. Development of IONM has contributed in exposure and localization of RLN during thyroidectomy. Furthermore, it decreases the rate of RLN injuries[54].

Visually intact nerve does not necessarily means it is functionally intact[55–57]. Even if RLN is anatomically intact during surgery complete avoidance of injury to the nerve cannot be guaranteed after the operation. Technique of IONM has enabled surgeons to recognize temporary injury to RLN intra-operatively and indicate early warning signs for surgical team to manoeuvre themselves to decrease or eliminate damage caused to the nerve. IONM can indicate non-dissociative injury such as injury from traction, clamping, electric cautery and suction.

IONM technique uses the principles of electrophysiology. Severity of injury to RLN is determined by monitoring the amplitude and latency of the VC EMG signal. Scott et al. concluded that decreased amplitude and increased latency is indication of nerve injury and the signal returns to normal if function of nerve is restored [60]. Tian et al. found significant relationship between RLN's temporary injury and extent of resection. Temporary injury to RLN risk during total thyroidectomy was three times greater than during right lobectomy[3]. Dralle et al. showed that permanent RLNP risk was significantly higher in lobectomy (1.34%) in comparison to subtotal resection (0.68%)[61,62]. These conclusions suggest that surgical teams should consider benefits and complications while deciding extent of the surgery. American Thyroid Association abbreviated as ATA guidelines of 2015 says that hemi-thyroidectomy may be sufficient for patients without clinically or radiologically involved cervical lymph node metastasis or extra-thyroidal extension[63,64].

The anatomy of right RLN is different than left RLN. Left RLN circles around aortic arch and travels almost vertically up to the trachea. Right RLN present around subclavian artery and travels obliquely towards the larynx[65]. A few researches have concluded differences between left and right RLN injury[60]. Tian et al. [66] study concluded, left RLN is more prone to surgical manipulation as compared to right RLN.

Normal quantitative parameters of IONM were analysed by a multi-centre study involving six centres[8]**,** it showed that the right vagus nerve implied a significantly larger median amplitude ($P<0.001$) and a significantly shorter latency ($P<0.001$) compared to the left vagus nerve. Phelan et al. concluded[8] that right and left RLN latencies were comparable. Latency of right vagus nerve was less than left vagus nerve but the difference was not very significant. Latency of RLN was significantly less as compared to vagus nerve. Amplitude of left vagus nerve was prominently less than right vagus nerve. However, between men and women, there was no difference in the amplitude of either the RLNs or the vagus nerves [60]. Another study concluded that the main latency of left vagus nerve was significantly more than right vagus nerve[67].

Among the two major categories of IONM,C-IONM is considered superior and more effective in preventing damage to RLN as compared toI-IONM[67].Study by Andres et al.[13] on 101 cases recorded with c-IONM in neck surgeries,13 patients showed temporary loss of signal. After changing the surgical approach LOS was prevented and recovered. In 3 cases LOS occurred due to placement of electrode on vagus nerve (3/101).In 1 case LRNP persisted even after 6 months due to anterior branch of RLN's accidental section (1/101 =1%). Vagus nerve was intact in all 3 cases; this trauma's exact reason is unclear but might be due to peri-neural bleeding or tractionto the nerve while exposing it. A study by Brauckhoff et al. [11] cites 2 cases of loss of signal in high-risk surgery by the electrode, 1 case was due to perineural bleeding at the time of placement of the electrode, and the other case was caused by torsion of the electrode which remained undetected. Mangano et al. [8,9,47] reported increase in size of vagus nerve after placement of electrode of 0.82 mm and dislocation rate of electrode per procedure was 11%. Therefore, it highlights the importance of suitable electrode size selection and careful use of standardised technique for electrode placement on the nerve. The studies made us believe that loss of signal may be due to the upward traction caused by right-angel dissector, necessary for electrode placement, used for 360° nerve dissection. In addition to c-IONM signal from the electrode, it is necessary to check signal of vagus nerve proximal to electrode placement after surgery. Furthermore, it can be assumed that some traction injuries during I-IONM cases could have been avoided if c-IONM had been used. This assumption is based on the findings from other studies reporting events to be reversible when instantly corrective measures were applied intra-operatively [67].

CONCLUSIONS

IONM can decrease the incidence of permanent RLNP rates. IONM is recommended in bilateral operations and malignancy cases. The benefit of this technique in the re-operation cases needs to be further explored[68]. Among the two types of IONM, c-IONM is superior as it provides real-time monitoring of the RLN function, allowing surgeon to adapt surgical manoeuvres to decrease the incidence of RLNP intra-operatively. The risk-benefit ratio of c-IONM should be further evaluated as it indicates a risk at electrode placement. This technique is particularly useful in operations where the RLN is difficult to identify by the standard lateral approach for example redo surgeries, posterior nodule surgeries, large and/or retrosternal goiter or in some rare cases when RLN is invaded by a tumor.

In large or retrosternal goitre superior approach to reach RLN is favoured[68]. When using c-IONM, at the end of the procedure, to ensure functional integrity of the vagal nerve and RLN, vagal stimulation proximal to site of electrode placement should be done. It is also important to perform in order to avoid false negative IONM result. IONM has augmented the precision in signaling the nerve injury early on and in accurately predicting post-operative vocal cord palsy. This enables young surgeons to withdraw surgical maneovers causing the nerve injury and in turn hone their surgical skills. IONM has turned into a powerful and affective risk minimisation technique used in thyroid surgeries since 2010s. This technology needs to keep pace with the endoscopic and robotic surgeries which are gaining momentum and popularity in the Western Hemisphere.

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