Continuous Intraoperative Nerve Monitoring in Thyroidectomies: A Systematic Review and Meta-Analysis

Dominic Ku1*, Michelle Hui1, Phylannie Cheung1,2, Mark Smith1,2, Faruque Riffat1,2, Niranjan Sritharan1,2, Dipti Kamani3 and Gregory Randolph1,4

1Department of Otolaryngology Head & Neck Surgery, Westmead Hospital, Sydney, Australia
2Department of Otolaryngology Head & Neck Surgery, Nepean Hospital, Sydney, Australia
3Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA
4Division of Surgical Oncology, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Objective: Application of intermittent intra-operative nerve monitoring (I-IONM) as an aid in thyroidectomies is common practice worldwide. While I-IONM is significantly beneficial in thyroid surgeries, it is limited by its intermittent nature, thereby allowing the recurrent laryngeal (RLN) nerve to be at risk of injury in-between stimulations. In the last decade, the introduction of continuous intraoperative RLN monitoring (CIONM) has overcome this limitation by enabling the operator to verify the functional integrity of the vagus nerve-recurrent laryngeal nerve (VN-RLN) axis in real-time. We aim to present the current evidence on CIONM utility for thyroid surgery by conducting the first meta-analysis on this technique.

Methods: A systematic review of literature was conducted by two independent reviewers via Ovid in the Medline, EMBASE and Cochrane reviews databases. The search was limited to human subject research in peer-reviewed articles of all languages published between Jan 1946 and April 2019. Medical subject headings (MeSH) terms utilised were thyroid surgery, thyroidectomies, recurrent laryngeal nerve, vagal nerve, monitor and stimulation. Thirty-eight papers were identified from Ovid, another six papers were identified by hand-search. A random effect meta-analysis was performed with assessment of heterogeneity using the $I^2$ value.

Results: A total of 23 papers that utilised continuous vagal nerve monitoring during thyroid surgery were identified. The proportion of temporary and permanent recurrent laryngeal nerve paralysis post-operation was 2.5% (95% CI 1.7-3.2%, $I^2 = 37.7$). The proportion of patients with permanent recurrent laryngeal nerve palsy post-operation was 0.05% (95% CI 0.08 - 0.2%, $I^2 = 0$).

Conclusion: CIONM is a safe and effective means by which RLN paralyses in thyroid surgery can be reduced.

Keywords

Thyroidectomy, Surgery, Nerve monitoring, Vagal nerve, Recurrent laryngeal nerve, Nerve paralysis, Nerve palsy

Introduction

Continuous intraoperative nerve monitoring (CIONM) via continuous vagal nerve stimulation for thyroid and parathyroid surgeries is a technology widely available throughout the past decade. Nevertheless, it has yet to be adopted as a routinely utilised adjunct to the established technique of intermittent intraoperative recurrent laryngeal nerve monitoring and direct visualisation. Although demonstrated to be a safe and effective technique of nerve monitoring in multiple centres [1-11], this study aims to demonstrate the summative result of this data in a meta-analysis of CIONM-related recurrent laryngeal nerve outcomes in thyroid surgery.

Since the introduction of recurrent laryngeal nerve monitoring (RLN) in thyroid surgery as an adjunct to direct visualisation, permanent vocal cord paralysis (VCP) has been greatly reduced in uncomplicated primary surgery [12,13]. With the use of intermittent intraoperative nerve monitoring
(I-IONM), rates of temporary VCP range between 1% to 9% and rates of permanent VCP range between 0% to 3% [14]. However, in revision surgery or surgery in more complex cases such as thyroid cancer surgery and Graves’ disease, the paralysis rates may be as high as 20% [15,16]. In cases where there is a loss of signal from the RLN on the first side of resection, a two-staged procedure has been strongly advocated to avoid the dire consequence of bilateral RLN paralysis [17,18]. This adverse outcome is estimated at 0.4%, and carries with it a potential risk of emergency airway surgery such as tracheostomy and intensive care admission [19].

The use of indirect RLN monitoring by vagal nerve stimulation ensued as authors realised the possibility of missing an injury distal to the point of direct RLN stimulation [20-22]. This principle was confirmed by Thomusch, et al. from prospectively collected data of more than 1500 nerves at risk, demonstrating the superior reliability of indirect IONM stimulation compared to direct RLN stimulation (p < 0.05, specificity of 97.6%, negative predictive value 99.6%) [23].

A methodical shortcoming has always existed for I-IONM in that the RLN remains at risk of damage between two manual stimulations. Efforts in developing continuous real-time nerve monitoring were first published by Lamade, et al. in 2007 [24]. The group first developed a double-balloon electromyography tube prototype and later a tripolar hybrid cuff electrode embedded in a silicone cuff which enabled continuous uninterrupted nerve monitoring by low current stimulation [25]. Later in 2009, Schneider, et al. developed a bipolar anchor electrode placed in contact with the vagal nerve between the common carotid artery and internal jugular vein [26]. Currently, one of the more popular systems utilised is the Automatic Periodic Stimulation (APS) electrodes (Medtronic, Minnesota, USA) which are placed on the vagal nerves, in conjunction with the Nerve Integrity Monitoring Electromyogram (NIM EMG) endotracheal tube (Medtronic).

These systems utilise electromyography (EMG) enabling real-time feedback of the entire Vagal-RLN axis. While I-IONM aids in identifying the RLNs, thereby reducing the chance of nerve transection, CIONM can detect early EMG changes that are associated with imminent nerve injuries, thus preventing nerve injuries caused by mechanical, thermal or cumulative trauma by forewarning the surgeons of impending nerve injury and allowing the surgeons to perform corrective manoeuvres [26].

Studies advocating for the use of CIONM point to the inherent disadvantage of I-IONM: Its inability to alert circuit discontinuity; effectively only able to prevent potential RLN injury until the nerve is stimulated after such injury has been caused. Authors championing the use of CIONM highlight the very point of injury prevention by early detection of nerve stress detected by electromyography [2]. CIONM equips the surgeon with knowledge of real-time functional status of RLN, thus allowing for immediate adjustment of surgical manoeuvres and pivotal intraoperative decision making such as a staged contra lateral thyroidectomy where the integrity of the RLN on the first side is uncertain [27]. With the availability of technology and data, the onus is on the surgeon to provide the best care available to minimise adverse events. In this study, we aim to report the rate of VCP in studies utilising CIONM for thyroid surgery. We hypothesise that the use of CIONM would lead to comparable or lower rates of RLN injury when compared to I-IONM alone.

### Materials and Methods

#### Search strategy

This meta-analysis had the primary objective of evaluating the role of CIONM on rates of RLN injury in subjects undergoing thyroid surgery. Our secondary goal was assessing other adverse events associated with CIONM. Articles published in all languages were searched via The Cochrane Collaboration Library, Medline and EMBASE database from Jan 1946 to April 2020. The following search strategy was used: #1, thyroid gland or thyroidectomy; #2, recurrent laryngeal nerve; #3, vagus nerve or vagal; #4, monitor’ or Stimulat’ or stimulat’; #2 or #3 (526032 articles) which is #5, #4 and #5 (59684 articles) which is #6, then #1 and #6 (475 articles). After duplicates were removed, there were 383 articles (Table 1). Another 5 articles were in-
Records identified through database searching (n = 475)

Additional records identified through other sources (n = 5)

Records after duplicates removed (n = 388)

Records excluded (n = 318)

Records screened (n = 77)

Full-text articles assessed for eligibility (n = 36)

Studies included in qualitative synthesis (n = 26)

Studies included in quantitative synthesis (Meta-analysis) (n = 23)

Figure 1: A total of twenty-three papers representing 3040 patients who underwent thyroidectomies with continuous intraoperative vagal nerve monitoring.

Study selection and data extraction

The abstracts were reviewed by two authors (DK and MH) independently with predefined inclusion and exclusion criteria according to the PRISMA guidelines (refer to PRISMA flowchart for reference, Figure 1). The selection of studies was guided by the PICOS principle as per PRISMA guidelines. Inclusion criteria were as follows, Patients: Undergone thyroid surgery, Intervention: CIONM, Comparisons: I-IONM or direct visualisation, Outcomes: Temporary and permanent VCP, Study design: Retrospective or prospective clinical trials. Exclusion criteria were as follows: Non-human studies, articles not reporting rates of temporary or permanent recurrent laryngeal paralysis rates, case series less than 5 patients. Uncertainties or conflicts were resolved by review of the full paper and discussion among the reviewers and other authors. Data was extracted from the articles and collected on a spreadsheet. Studies with reporting on the same population were identified, and results extracted once only so that they were not replicated.

Risk of bias assessment

The risk of bias for each eligible study was independently assessed by two review authors (DK and MH). Prospective cohort studies and retrospective cohort studies were assessed by the ACROBAT-NRSi Cochrane Risk of Bias Tool [28]. The seven domains including confounding, selection of participants, classification of interventions, deviations from intended intervention, missing data, measurement of outcomes and selection of reported results were assessed and categorised into low, moderate, severe, or unclear risk of bias. An overall assessment of risk of bias for each study was reported as low, moderate, serious, critical of no information on the risk of bias.

Primary and secondary outcomes

Our primary outcomes were defined a priori and included temporary and permanent vocal cord paralysis (VCP) rates,
whilst our secondary outcomes were any monitoring related adverse events. Rates of VCP were calculated by recording number of paralysed nerves over total number of nerves at risk. Temporary VCP was differentiated from permanent VCP by the final follow-up status of vocal cords as observed by fiberoptic examination, which was at three months for the majority of the published articles. Patient age, gender and proportion of cases with Graves’ disease, thyroiditis and thyroid cancer were recorded if reported. Secondary outcomes reported were defined as side-effects of CIONM, such as mechanical nerve injury or autonomic disturbances such as bradycardia, arrhythmias and hemodynamic instability.

Statistical analysis

Meta-analysis was performed using a random effect model and assessed with the I² value with RStudio (version 1.3.1093) [29]. Rates of temporary and permanent VCP were aggregated with effect size calculated as a function of events (temporary or permanent VCP over the total number of nerves at risk. The calculation of the standard error, variance and 95% confidence intervals assume the effect size calculated follows a normal distribution, which is true for increasingly large sample sizes (based on the Central Limit Theorem). For smaller sample sizes, the distribution of the effect size may well be skewed, and hence the calculation of the confidence intervals may result in a negative value for the lower limit. Based on the formula of heterogeneity [16], I² was used to quantify heterogeneity of rates of temporary and permanent VC paralysis in the studies. The interpretation of I² < 0 is the same as that of I² = 0. Negative values of I² are rounded up to zero, and interpreted as no observed heterogeneity [30]. The heterogeneity was low among the studies, hence fixed effect model was employed.

Results

A total of 23 papers were included for the systematic review from the initial search result of 440 papers (see Figure 1 for PRISMA flowchart). These papers consisted of 7 retrospective cohort studies and 15 prospective cohort studies published and one prospective randomised controlled trial between the years 2007 and 2019 (Table 2).

Risk of bias assessment for included studies

The risk of bias assessment for all 23 studies is presented in Table 3. Most studies exhibited moderate risk of bias according to the seven categories of assessment. The most prevailing feature of bias appeared to be the high variability in operations, including benign, malignant and revision surgeries as well as lobotomy, hemithyroidectomy, total thyroidectomy and neck dissections. The variability in pathology and operation in the studies may increase the risk of bias in reporting the efficacy of CIONM in thyroid surgery. There is a significant risk of publication bias. This review of literature has only identified one article by Terris, et al. reporting a termination of a study due to the adverse events directly from CIONM [31].

Patient characteristics

A total of 3040 patients and 5007 nerves at risk were reported to have undergone continuous intraoperative vagal nerve monitoring in the context of thyroid surgery. We observed a female preponderance with 76.4% females in the patient population. The mean age of patients ranged from 38 to 61 years of ageing the adult population, and one paper reported on a paediatric population between 4 to 18 years of age [32] (Table 2).

A significant proportion of papers did not report important patient diagnosis for the CIONM groups i.e. Graves’ disease, thyroiditis or thyroid cancer specifically, albeit having reported it for the overall study (Table 2). However, most papers note that patients at higher risk of nerve paralysis were generally selected for CIONM. There were various definitions of high risk procedures; Yu, et al. denoted six patient groups: 1) Revision surgery, 2) Pre-existing unilateral VCP undergoing bilateral thyroidectomy or contralateral thyroidectomy, 3) Involves retrosternal goitre, 4) Suspected bilateral multiple carcinomas, 5) Suspected large carcinomas with dorsal extension invading into surrounding tissue and 6) Graves’ disease patients [10].

Vagal nerve stimulation apparatus

The papers from our systematic review spanned over two decades, reflecting the evolution of direct vagal nerve stimulation apparatus. Although most centres utilised a handheld bipolar stimulation probe for intermittent direct stimulation of the vagal nerve (VN) and RLN, a number of different designs were tried out for CIONM of the VN. The pioneering studies by Lamade and Ulmer, et al. [30,31] in conjunction with the Fraunhofer Institute and Inomed constructed a tripolar silicone cuff electrode that enveloped the VN longitudinally [25,33]. This group, in association with the IKONA consortium, later developed a saxophone-shaped back strap tripolar stimulation electrode [34-36].

In 2007, Schneider, et al. introduced another vagal nerve stimulator developed in cooperation with Bioprocessing and Analytical Measurement Techniques (Heiligenstadt, Germany) and Dr. Langer Medical Gmb H. This was a t-shaped electrode that anchored between the carotid vessels and the vagal nerve after dissecting the carotid sheath for about 2 cm.

Since then, the majority of the remaining papers (12 of 15) reported the use of the Automatic Periodic Stimulation (APS) VN stimulator (2.0 or 3.0 mm, Medtronic, Jacksonville, FL, USA). Although first reported by Vlastarakos and Mochloulis, et al. in 2011 [37], it was Schneider and Randolph, et al. who published the first cohort study with the use of this device. The APS system generates a continuous electrical pulse during the operation (10 per min, 100 µs, 1 mA) [38].

Vocal cord paralysis rates

This meta-analysis focuses on temporary and permanent vocal cord paralysis rates in the reviewed papers, the combined events are displayed in a forest plot (Figure 2). The accumulative data from papers published between 2007 and 2019 were analysed using a random effect model. The proportion of patients with temporary and permanent VCP were 2.5% (95% CI 1.7-3.2%, I² = 37.7) (Table 4). The proportion of
### Table 2: Demographic characteristics of studies.

| Author                  | Country                  | Study type                          | Number of patients | Nerves at risk | Mean Age (years) | Females n (%) |
|-------------------------|--------------------------|-------------------------------------|--------------------|----------------|------------------|---------------|
| Lamade, 2000 [24]       | Stuttgart, Germany       | Prospective cohort                  | 7                  | 12             | 48               | -             |
| Ulmer, 2008 [13]        | Stuttgart, Germany       | Prospective cohort                  | 19                 | 31             | 51               | 16 (79)       |
| Schneider, 2009 [26]    | Leipzig, Germany         | Prospective cohort                  | 4                  | 5             | 51               | 15 (78)       |
| Jonas, 2016 [41]        | Frankfurt, Germany       | Prospective cohort                  | 100                | 188           | 54               | 56 (76)       |
| Lamade, 2011 [35]       | Stuttgart, Germany       | Prospective cohort                  | 11                 | 13            | 58               | 17 (96)       |
| Lamade, 2011 [35]       | Stuttgart, Germany       | Prospective cohort                  | 24                 | 30            | 51               | 13 (59)       |
| Ulmer, 2008 [33]        | Stuttgart, Germany       | Prospective cohort                  | 19                 | 31            | 51               | 15 (79)       |
| Schneider, 2009 [26]    | Leipzig, Germany         | Prospective cohort                  | 4                  | 5             | 51               | 15 (78)       |
| Jonas, 2016 [41]        | Frankfurt, Germany       | Prospective cohort                  | 100                | 188           | 54               | 56 (76)       |
| Lamade, 2011 [35]       | Stuttgart, Germany       | Prospective cohort                  | 11                 | 13            | 58               | 17 (96)       |
| Lamade, 2011 [35]       | Stuttgart, Germany       | Prospective cohort                  | 24                 | 30            | 51               | 13 (59)       |
| Ulmer, 2008 [33]        | Stuttgart, Germany       | Prospective cohort                  | 19                 | 31            | 51               | 15 (79)       |
| Schneider, 2009 [26]    | Leipzig, Germany         | Prospective cohort                  | 4                  | 5             | 51               | 15 (78)       |
| Jonas, 2016 [41]        | Frankfurt, Germany       | Prospective cohort                  | 100                | 188           | 54               | 56 (76)       |
| Lamade, 2011 [35]       | Stuttgart, Germany       | Prospective cohort                  | 11                 | 13            | 58               | 17 (96)       |
| Lamade, 2011 [35]       | Stuttgart, Germany       | Prospective cohort                  | 24                 | 30            | 51               | 13 (59)       |
| Lamade, 2011 [35]       | Stuttgart, Germany       | Prospective randomised study        | 22                 | 44            | 51               | 13 (59)       |
| Koulouris, 2012 [36]    | Thessaloniki, Greece     | Prospective cohort                  | 22                 | 44            | 51               | 13 (59)       |
| Friedrich, 2012 [36]    | Halle, Germany; Boston, USA | Prospective cohort                  | 100               | 180           | 51               | 82 (82)       |
| Schneider, 2012 [38]    | Halle, Germany; Boston, USA | Retrospective cohort study          | 38                 | 78            | 51               | 13 (78)       |
| Van Slyke, 2013 [9]     | Aalst, Belgium           | Prospective cohort                  | 101                | 180           | 51               | 82 (82)       |
| Schwartz, 2013 [39]     | Halle, Germany; Boston, USA | Retrospective cohort study          | 38                 | 78            | 51               | 13 (78)       |
| Kandil, 2018 [50]       | Halle, Germany           | Retrospective cohort study          | 105                | 175           | 73               | 73 (73)       |
| De la Quintana Basarate, 2018 [15] | New Orleans, USA, Retroreflective cohort | 344                | 63            | 37               | 277 (83)       |
| Hamilton, 2019 [6]      | Halle, Germany           | Retrospective cohort study          | 105                | 175           | 73               | 73 (73)       |
| Yu, 2019 [10]           | Halle, Germany           | Retrospective cohort study          | 248                | 63            | 37               | 277 (83)       |
| Zhou, 2019 [11]         | Harbin, China            | Retrospective cohort study          | 105                | 175           | 73               | 73 (73)       |
| Hamilton, 2019 [6]      | Halle, Germany           | Retrospective cohort study          | 105                | 175           | 73               | 73 (73)       |
| Yu, 2019 [10]           | Halle, Germany           | Retrospective cohort study          | 248                | 63            | 37               | 277 (83)       |
| Zhou, 2019 [11]         | Harbin, China            | Retrospective cohort study          | 105                | 175           | 73               | 73 (73)       |
| Hamada, 2019 [11]       | Harbin, China            | Retrospective cohort study          | 105                | 175           | 73               | 73 (73)       |
Table 3: Risk of bias assessment of the 23 included studies.

| Author            | Confounding | Classification of interventions | Deviations from intended interventions | Measurement of outcomes | Missing data | Overall |
|-------------------|-------------|----------------------------------|----------------------------------------|-------------------------|--------------|---------|
| Lamade, 2000 [24] | Low         | Moderate                          | Varied operations;                   | Low                     | Low          | Moderate |
| Ulmer, 2008 [33]  | Low         | Moderate                          | Low                                    | Low                     | Low          | Moderate |
| Schneider, 2009 [26] | Moderate 1 | Moderate                          | Low                                    | Low                     | Low          | Moderate |
| Jonas, 2011 [35]  | Moderate 2 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Lamade, 2011 [36] | Moderate 3 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Koibun, 2012 [37] | Moderate 4 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Schneider, 2013 [38] | Moderate 5 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Lamade, 2013 [39] | Moderate 6 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Ulmer, 2014 [40]  | Moderate 7 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Teris, 2015 [41]  | Moderate 8 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Fischer, 2016 [42] | Moderate 9 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Koulouris, 2017 [43] | Moderate 10 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Schneider, 2018 [44] | Moderate 11 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Adamczewski, 2019 [45] | Moderate 12 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Marin Arteaga, 2020 [46] | Moderate 13 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Julien, 2021 [47]  | Moderate 14 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Schneider, 2022 [48] | Moderate 15 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| De la Quintana Basarrate, 2023 [49] | Moderate 16 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Hamilton, 2024 [50] | Moderate 17 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Yu, 2025 [51]     | Moderate 18 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |
| Zhou, 2026 [52]   | Moderate 19 | Moderate                          | Moderate                               | Low                     | Low          | Moderate |

1 Varied operations; 2 Mix of benign and malignant pathologies and revision surgery; 3 Insufficient report of patient demographics and risk profile; 4 Unclear delineation of I-IONM and CIONM; 5 Unclear reporting of VCP according to mode RLN monitoring; 6 Multi-centre study; 7 Only a small subset of a large cohort undergone CIONM was reported; 8 Retrospective review of large cohorts; 9 Minimal reporting on type of surgery and pathology encountered.
The percentage of combined events (temporary and permanent VCP) displayed.

Table 4: All studies - Overall VC paralyses (combined temporary and permanent VC paralyses) (NAR = Nerves at risk, VC = Vocal cord).

| Study                  | Events Number, (%) NAR Number |
|------------------------|-------------------------------|
| Lamade, 2000 [24]      | 0 (0) 7                       |
| Ulmer, 2008 [33]       | 0 (0) 19                      |
| Schneider, 2009 [26]   | 1 (1.3) 78                   |
| Jonas, 2016 [41]       | 3 (16.7) 188                 |
| Lamade, 2011 [35]      | 0 (0) 13                     |
| Lamade, 2011 [35]      | 0 (0) 30                     |
| Friedrich, 2012 [36]   | 0 (0) 22                     |
| Koulouris, 2012 [39]   | 7 (2) 348                    |
| Schneider, 2013 [38]   | 4 (7.7) 52                   |
| Van Slycke, 2013 [9]   | 4 (2.2) 180                  |
| Phelan, 2014 [40]      | 6 (2.9) 204                  |
| Brauckhoff, 2016 [43]  | 4 (4.6) 87                   |
| Terris, 2015 [31]      | 2 (16.7) 12                  |
| Adamczewski, 2015 [4]  | 1 (2.5) 40                   |
| Schneider, 2015 [14]   | 33 (2.3) 1314                |
| Marin Arteaga, 2017 [8]| 6 (3.8) 159                  |
| Julien, 2017 [7]       | 0 (0) 14                     |
| Schneider, 2018 [32]   | 28 (41.2) 68                 |
| Kandil, 2018 [50]      | 15 (3.3) 455                 |
| De la Quintana Basarrate, 2018 [5] | 8 (2) 400 |
| Hamilton, 2019 [6]     | 8 (3.1) 256                  |
| Yu, 2019 [10]          | 2 (1.2) 173                  |
| Zhou, 2019 [11]        | 4 (2.8) 144                  |

Proportion of temporary and permanent VC palsies is 2.5% (95% CI 1.7-3.2%, $I^2 = 37.7$)

patients with permanent VCP was 0.05% (95% CI 0.08-0.2%, $I^2 = 0$) (Table 5).

The papers which utilised the APS (Medtronic) VN stimulator were further analysed separately. The proportion of patients with temporary and permanent VCP was 0.59% (95% CI 0.23-0.94%, $I^2 = 0$) (Table 6). The proportion of patients with permanent VCP was 0.08% (95% CI 0-0.32%, $I^2 = 38.9$) (Table 7).

There was one paper which reported two cases of bilateral VCP requiring emergency tracheostomy and tracheostomy tube for 15 days. Both patients had recovery of their
Table 5: All studies: Permanent VC paralyses (numbers, %) (NAR = Nerves at risk, VC = Vocal cord).

| Study                      | Events number, (%) | NAR Number |
|----------------------------|--------------------|------------|
| 1 Lamade, 2000 [24]        | 0                  | 7          |
| 2 Ulmer, 2008 [33]         | 0                  | 19         |
| 3 Schneider, 2009 [26]     | 0                  | 78         |
| 4 Jonas, 2016 [41]         | 1 (0.5)            | 188        |
| 5 Lamade, 2011 [35]        | 0                  | 13         |
| 6 Lamade, 2011 [35]        | 0                  | 30         |
| 7 Friedrich, 2012 [36]     | 0                  | 22         |
| 8 Koulouris, 2012 [39]     | 0                  | 348        |
| 9 Schneider, 2013 [38]     | 0                  | 52         |
| 10 Van Slycke, 2013 [9]    | 1 (0.6)            | 180        |
| 11 Phelan, 2014 [40]       | 0                  | 204        |
| 12 Brauckhoff, 2016 [43]   | 1 (1.1)            | 87         |
| 13 Terris, 2015 [31]       | 0                  | 12         |
| 14 Adamczewski, 2015 [4]   | 0                  | 40         |
| 15 Schneider, 2015 [14]    | 0                  | 1314       |
| 16 Marin Arteaga, 2017 [8] | 1 (0.6)            | 159        |
| 17 Julien, 2017 [7]        | 0                  | 14         |
| 18 Schneider, 2018 [32]    | 0                  | 68         |
| 19 Kandil, 2018 [50]       | 0                  | 455        |
| 20 De la Quintana Basarrate, 2018 [5] | 0 | 400 |
| 21 Hamilton, 2019 [6]      | 2 (0.8)            | 256        |
| 22 Yu, 2019 [10]           | 0                  | 173        |
| 23 Zhou, 2019 [11]         | 0                  | 144        |

Proportion of permanent VC palsies is 0.05% (95% CI 0.08-0.2%, I² = 0).

Table 6: Studies using APS electrode only (Medtronic): Overall VC paralyses (combined temporary and permanent VC paralysis) (NAR = Nerves at risk, VC = Vocal cord).

| Study                      | Events Number, (%) | NAR Number |
|----------------------------|--------------------|------------|
| 1 Schneider, 2013 [38]     | 4 (7.7)            | 52         |
| 2 Phelan, 2014 [40]        | 5 (2.5)            | 204        |
| 3 Brauckhoff, 2016 [43]    | 4 (4.6)            | 87         |
| 4 Terris, 2015 [31]        | 1 (8.3)            | 12         |
| 5 Schneider, 2015 [14]     | 33 (2.5)           | 1314       |
| 6 Marin Arteaga, 2017 [8]  | 7 (4.4)            | 159        |
| 7 Julien, 2017 [7]         | 0                  | 14         |
| 8 Schneider, 2018 [32]     | 2 (2.9)            | 68         |
| 9 Kandil, 2018 [50]        | 0                  | 455        |
| 10 Hamilton, 2019 [6]      | 8 (3.1)            | 256        |
| 11 Yu, 2019 [10]           | 2 (1.2)            | 173        |
| 12 Zhou, 2019 [11]         | 4 (2.8)            | 144        |

Proportion of temporary and permanent VC palsies is 0.59% (95% CI 0.23-0.94%, I² = 0).

Table 7: Studies using APS electrode only (Medtronic): Permanent VC paralyses (NAR = Nerves at risk, VC = Vocal cord).

| Study                      | Events Number, (%) | NAR Number |
|----------------------------|--------------------|------------|
| 1 Schneider, 2013 [38]     | 0                  | 52         |
| 2 Phelan, 2014 [40]        | 0                  | 204        |
| 3 Brauckhoff, 2016 [43]    | 1 (1.1)            | 87         |
| 4 Terris, 2015 [31]        | 0                  | 12         |
| 5 Schneider, 2015 [14]     | 0                  | 1314       |
| 6 Marin Arteaga, 2017 [8]  | 1 (0.6)            | 159        |
| 7 Julien, 2017 [7]         | 0                  | 14         |
| 8 Schneider, 2018 [32]     | 0                  | 68         |
| 9 Kandil, 2018 [50]        | 0                  | 455        |
| 10 Hamilton, 2019 [6]      | 2 (0.8)            | 256        |
| 11 Yu, 2019 [10]           | 0                  | 173        |
| 12 Zhou, 2019 [11]         | 0                  | 144        |

Proportion of permanent VC palsies is 0.08% (95% CI 0-0.32%, I² = 38.9).

VC function in the next 3 months. Both cases had intact neuromonitoring tracings and the paralyses were attributed to incorrect placement of tracheal tube inflatable cuffs over the vocal cords [39].

Safety of VN stimulation during CIONM

The majority of the papers in this review have reported safe use of VN stimulation without autonomic disturbances when stimulation currents and frequencies were kept low [10,40-42]. The safety of CIONM was also established in paediatric populations [32] and high-risk populations such as those with advanced atrioventricular blocks [2]. However, there were instances of adverse effects reported in a minority of cases. Terris, et al. reported two cases of complications directly related to the application of VN monitoring in a series that was abruptly ceased due to the perceived increased risk of CIONM. This paper reported one case of temporary vagal nerve paralysis secondary to VN electrode dislodgement, and a case of hemodynamic instability manifested in bradycardia and hypotension in the initial phase of surgery shortly after calibration. Subsequently, Brauckhoff, et al. also reported electrode related VN injury resulting in temporary VN paralysis in a minority of patients (2 nerves, 2% nerves at risk) [43]. Marin Arteaga, et al. reported similar rates of temporary VN paralysis (3 nerves, 1.9% nerve at risk). The authors postulated this could be caused by traction when exposing the nerve or perineural bleeding, but no haematoma was visualised [8].

Discussion

This meta-analysis found no permanent vagal nerve palsy...
and only 6 cases of temporary vagal nerve palsy of a total of 5007 nerves at risk resulting from the use of CIONM. There was one reported case of haemodynamic instability by Terris, et al. resulting the use of VN monitoring [31]. The overall rate of VCP was 2.5% and a permanent rate of VCP was 0.05%. These aggregated results indicate lower VCP rates when compared to published data on I-IONM or visualisation alone.

Since the introduction of IONM to thyroid surgery, its benefits in expediting RLN identification, reducing RLN paralysis and avoidance of bilateral VCP has been realised [44]. The use of IONM via electromyography has been recommended as an option by the American Academy of Otolaryngology Clinical Practice guidelines since 2013 [45]. Furthermore, since 2011 the German Association of Endocrine Surgeons has recommended the use of IONM for all thyroid surgery, citing its additional utility in revision surgery and postoperative prognostication of neural function [46]. Furthermore, the use of IONM has equipped the surgical operator with knowledge of RLN function at key intraoperative decision points. The awareness of a loss of signal (LOS) on the initial side of thyroidectomy allows the surgical operator to delay contralateral thyroidectomy in a staged procedure, thereby reducing the dreaded complication of bilateral VC paralysis to near zero [18,47,48]. With proven utility, IONM has taken up an important role in optimising the safety of thyroidectomy surgery.

Nevertheless, the nature of intermittent stimulation used for I-IONM has two obvious design shortfalls. Firstly, it exposes the RLN to the risk of irreparable damage in between manual stimulations [49]. Secondly, I-IONM limits the assessment of nerve integrity to the site of direct nerve stimulation, wherein a more proximal RLN lesion may not be detected [18]. Conversely, the development of CIONM via vagal nerve stimulation enables real-time RLN monitoring along the entire nerve axis [38]. These strengths of CIONM adds to the arsenal of the thyroid surgeon facing cases with high risk of nerve injury. In our meta-analysis, Yu, et al. denoted six main high risk patient groups: 1) Revision surgery, 2) Pre-existing unilateral VCP undergoing bilateral thyroidectomy or contralateral thyroidectomy, 3) Involves retrosternal goitre, 4) Suspected cardinal type 1 LOS and global type 2 LOS. Segmental type 1 LOS was defined as a decrease of nerve amplitude to less than 100 microvolts (µV). This was further classified into segmental type 1 LOS and global type 2 LOS. Segmental type 1 LOS typically presents with a sudden loss of nerve amplitude and unchanged nerve latency, which is likely due to sudden stretching, haemostatic instruments used in proximity, pinching or transection of the nerve. Global type 2 LOS typically presents with a fluctuating loss of nerve amplitude, which is likely due to traction stress on the nerve and the damage is often reversible upon release of the nerve [42].

The successful application of CIONM is contingent on surgical expertise, equipment calibration, recognition of impending nerve injury and corresponding manoeuvres to alleviate potential damage to the RLN. Regardless of the manufacturers, the CIONM apparatus generally includes a multichannel EMG system, sensing endotracheal surface electrode, handheld stimulation electrode and direct VN electrode. In order to utilise CIONM proficiently, the surgeon must overcome the learning curve involved in both the technical application of CIONM apparatus and interpretation of EMGs. The detailed surgical techniques and calibration of various CIONM systems are described in other studies and are beyond the scope of this paper [1,52].

The fundamental advancement in CIONM is its ability to detect potential insult to the RLN, thereby allowing the surgeon to respond to this threat immediately, avoiding damage to the RLN [40]. This is expressed in EMG changes during CIONM. The surgeon must develop expertise in interpreting real-time EMG changes and act accordingly. Schneider, et al. have aptly summarised EMG changes and corresponding risk classification of potential RLN injury based on multiple large cohort trials and animal studies [40,42,50,52]. Impending nerve injury can be detected by EMG combined events (CE), which were defined as greater than 50% decrease in amplitude and concomitant greater than 10% increase in latency from baseline. Such insults have been shown to be caused mainly by traction and the reversal of related surgical manoeuvres have been shown to restore amplitude thus avoiding RLN injury in majority of cases (up to 80%) [14,38]. The ability to foresee potential injury and respond appropriately may explain the low rates of temporary and permanent paralyses observed in our meta-analysis when compared to conventional IONM alone (0.59% in the APS group compared to literature report of 2% in IONM [13].

Loss of signal (LOS) is more foreboding EMG changes. This was defined as a decrease of nerve amplitude to less than 100 microvolts (µV). This was further classified into segmental type 1 LOS and global type 2 LOS. Segmental type 1 LOS typically presents with a sudden loss of nerve amplitude and unchanged nerve latency, which is likely due to sudden stretching, haemostatic instruments used in proximity, pinching or transection of the nerve. Global type 2 LOS typically presents with a fluctuating loss of nerve amplitude, which is likely due to traction stress on the nerve and the damage is often reversible upon release of the nerve [42]. Good prognosticating factors for nerve recovery after LOS include slow onset of LOS, and the presence of and degree of intra-operative amplitude recovery [52].

During the operation, if there was a LOS and failure to regain 50% of baseline amplitude, there is a significant risk of early postoperative VCP (43). CIONM has a predictive accuracy of 99.5% and lower false positive and negative rates than IONM (0.3% vs. 0.5% and 0.2% vs. 0.6% respectively) [52]. Endowed with the dependable information CIONM provides, the surgical team is in optimal position for intraoperative decision making. We believe it is precisely due to the ability to continually confirm RLN status, and reliably predict postoperative RLN function that this meta-analysis has reported.
record low rates of temporary, permanent and bilateral vocal cord paralysis.

**Limitations**

This study aims to report on the current evidence for the use of CIONM in thyroid surgery. The data currently available in the literature is limited due to study design - there was only one randomised control trial for CIONM at present. There is a need to standardise data reporting in regard to patient demographics, pre- and intraoperative risk factors, intra-operative nerve monitoring and post-operative follow-up. Finally, this study reported from a relatively narrow range of institutions with several centres publishing multiple studies - it is difficult to separate the benefit tertiary centres and expert surgeons from the true effect of CIONM in thyroid surgery.

**Conclusion**

Continuous intraoperative vagal nerve monitoring has been shown to be a reliable and safe mechanism by which recurrent laryngeal nerve injury can be prevented, and thus, offer the best chance of optimal vocal cord function after thyroid surgery. With definitive data at hand, the surgical operator should consider the use of CIONM especially in high risk thyroidectomy procedures.

**Acknowledgements**

Statistical analysis was assisted by Mr Vikas K Sewani (B. Sci (Maths) BEng, PhD candidate at Centre for Quantum Computation and Communication Technology, Sydney Australia).

**References**

1. Schneider R, Machens A, Randolph G, et al. (2019) Impact of continuous intraoperative vagus stimulation on intraoperative decision making in favor of or against bilateral surgery in benign goiter. Best Pract Res Clin Endocrinol Metab 33: 101285.

2. Schneider R, Machens A, Bucher M, et al. (2016) Continuous intraoperative monitoring of vagus and recurrent laryngeal nerve function in patients with advanced atrioventricular block. Langenbecks Arch Surg 401: 551-516.

3. Dionigi G, Donatini G, Boni L, et al. (2013) Continuous monitoring of the recurrent laryngeal nerve in thyroid surgery: A critical appraisal. Int J Surg 11: S44-S46.

4. Adamczyzewski Z, Chwalkiewicz M, Lewinski A, et al. (2015) Continuous intraoperative neuromonitoring (CIONM) of the recurrent laryngeal nerve is sufficient as the only neuromonitoring technique in thyroidectomy performed because of benign goitre. Ann Agric Environ Med 22: 495-498.

5. De la Quintana Basarrate A, Iglesias Martinez A, Salutregui I, et al. (2018) Continuous monitoring of the recurrent laryngeal nerve. Langenbecks Arch Surg 403: 333-339.

6. Hamilton N, Morley H, Haywood M, et al. (2019) Continuous intraoperative nerve monitoring in thyroidectomy using automatic periodic stimulation in 256 at-risk nerves. Ann R Coll Surg Engl 101: 432-435.

7. Julien N, Ferrary E, Sokoloff A, et al. (2017) Vagal and recurrent laryngeal nerves neuromonitoring during thyroidectomy and parathyroidectomy: A prospective study. Eur Ann Otorhinolaryngol Head Neck Dis 134: 77-82.

8. Marin Arteaga A, Peloni G, Leuchter I, et al. (2018) Modification of the surgical strategy for the dissection of the recurrent laryngeal nerve using continuous intraoperative nerve monitoring. World J Surg 42: 444-450.

9. Van Slycke S, Gillardin JP, Brusselaers N, et al. (2013) Initial experience with S-shaped electrode for continuous vagal nerve stimulation in thyroid surgery. Langenbecks Arch Surg 398: 717-722.

10. Yu Q, Liu K, Zhang S, et al. (2019) Application of continuous and intermittent intraoperative nerve monitoring in thyroid surgery. J Surg Res 243: 325-331.

11. Zhou L, Dionigi G, Pontin A, et al. (2018) How does neural monitoring help during thyroid surgery for Graves’ disease? J Clin Transl Endocrinol 15: 6-11.

12. Eltzschig HK, Posner M, Moore FD (2002) The use of readily available equipment in a simple method for intraoperative monitoring of recurrent laryngeal nerve function during thyroid surgery: Initial experience with more than 300 cases. Arch Surg 137: 452-456.

13. Timmermann W, Hamelmann W, Thomusch O, et al. (2004) Effectiveness and results of intraoperative neuromonitoring in thyroid surgery. Statement of the Interdisciplinary Study Group on Intraoperative Neuromonitoring of Thyroid Surgery. Chirurg 75: 916-922.

14. Schneider R, Sekulla C, Machens A, et al. (2015) Postoperative vocal fold palsy in patients undergoing thyroid surgery with continuous or intermittent nerve monitoring. Br J Surg 102: 1380-1387.

15. Yarbrough DE, Thompson GB, Kasperbauer JL, et al. (2004) Intraoperative electromygographic monitoring of the recurrent laryngeal nerve in reoperative thyroid and parathyroid surgery. Surgery 136: 1107-1115.

16. Chan W-F, Lang BH-H, Lo C-Y (2006) The role of intraoperative neuromonitoring of recurrent laryngeal nerve during thyroidectomy: A comparative study on 1000 nerves at risk. Surgery 140: 866-873.

17. Drale H, Sekulla C, Lorenz K, et al. (2012) Loss of the nerve monitoring signal during bilateral thyroid surgery. Br J Surg 99: 1089-1095.

18. Schneider R, Randolph GW, Dionigi G, et al. (2018) International neural monitoring study group guideline 2018 part I: Staging bilateral thyroid surgery with monitoring loss of signal. Laryngoscope 128: S1-S17.

19. Cannizzaro MA, Bianco SL, Picardo MC, et al. (2017) How to avoid and to manage post-operative complications in thyroid surgery. Updates Surge 69: 211-215.

20. Lambert AW, Cosgrove C, Barwell J, et al. (2000) Vagus nerve stimulation: Quality control in thyroid and parathyroid surgery. J Laryngology Otol 114: 125-127.

21. Jonas J (2002) Reliability of intraoperative recurrent laryngeal nerve monitoring in thyroid surgery. Zentralbl Chir 127: 404-408.

22. Chiang FY, Lu IC, Kuo WR, et al. (2008) The mechanism of recurrent laryngeal nerve injury during thyroid surgery-the application of intraoperative neuromonitoring. Surgery 143: 743-749.

23. Thomusch O, Sekulla C, Machens A, et al. (2004) Validity of intra-operative neuromonitoring signals in thyroid surgery. Langenbeck’s Arch Surg 389: 499-503.

24. Lamade W, Meyding-Lamade U, Buchhold C, et al. (2000) First continuous nerve monitoring in thyroid gland surgery. Der Chirurg 71: 551-557.
25. Lamadé W, Ulmer C, Seimer A, et al. (2007) A new system for continuous recurrent laryngeal nerve monitoring. Minim Invasive Ther Allied Technol 16: 149-154.

26. Schneider R, Przybyl J, Hermann M, et al. (2009) A new anchor electrode design for continuous neuromonitoring of the recurrent laryngeal nerve by vagal nerve stimulations. Langenbeck’s Arch Surg 394: 903-910.

27. Schneider R, Randolph G, Dionigi G, et al. (2019) Prediction of postoperative vocal fold function after intraoperative recovery of loss of signal. The Laryngoscope 129: 525-531.

28. Sterne J, Higgins J, Reeves B, et al. (2014) A cochrane risk of bias assessment tool: for non-randomized studies of interventions (ACROBAT-NRSI), Version 1.0. 0, 1-96.

29. Heeke C, Kampisiou C, Niemeyer H, et al. (2017) A systematic review and meta-analysis of correlates of prolonged grief disorder in adults exposed to violent loss. Eur J Psychotraumatol 10: 1583524.

30. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat med 21: 1539-1558.

31. Terris DJ, Chaung K, Duke WS (2015) Continuous vagal nerve monitoring is dangerous and should not routinely be done during thyroid surgery. World J Surg 39: 2471-2476.

32. Schneider R, Machens A, Sekulla C, et al. (2018) Twenty-year experience of paediatric thyroid surgery using intraoperative nerve monitoring. Br J Surg 105: 996-1005.

33. Ulmer C, Koch KP, Seimer A, et al. (2008) Real-time monitoring of the recurrent laryngeal nerve: An observational clinical trial. Surgery 143: 359-365.

34. Lamadé W, Ulmer C, Friedrich C, et al. (2011) Signal stability as key requirement for continuous intraoperative neuromonitoring. Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizin 82: 913-920.

35. Lamade W, Ulmer C, Rieber F, et al. (2011) New backstrap vagus electrode for continuous intraoperative neuromonitoring in thyroid surgery. Surg Innov 18: 206-213.

36. Friedrich C, Ulmer C, Rieber F, et al. (2012) Safety analysis of vagal nerve stimulation for continuous nerve monitoring during thyroid surgery. Laryngoscope 122: 1979-1987.

37. Vlastarakos PV, Kenway B, Mochloulis G (2012) Vagal versus re-current laryngeal nerve monitoring in thyroid surgery. Eur Arch Otorhinolaryngol 269: 1305-1306.

38. Schneider R, Randolph GW, Sekulla C, et al. (2013) Continuous intraoperative vagus nerve stimulation for identification of imminent recurrent laryngeal nerve injury. Head Neck 35: 1591-1598.

39. Koulouris C, Papavramidis TS, Plakos I, et al. (2012) Intraoperative stimulation neuromonitoring versus intraoperative continuous electromyographic neuromonitoring in total thyroidectomy: identifying laryngeal complications. Am J Surg 204: 49-53.

40. Phelan E, Schneider R, Lorenz K, et al. (2014) Continuous vagal IONM prevents recurrent laryngeal nerve paralysis by revealing initial EMG changes of impending neuropraxic injury: A prospective, multicenter study. Laryngoscope 124: 1498-1505.

41. Jonas J (2016) Signal changes of continuous intraoperative neuromonitoring in thyroid resections with postoperative vocal cord palsy. Zentralbl Chir 141: 170-174.

42. Schneider R, Sekulla C, Machens A, et al. (2016) Dynamics of loss and recovery of the nerve monitoring signal during thyroidectomy my predict early postoperative vocal fold function. Head Neck 38: E1144-E1151.

43. Brauckhoff K, Vik R, Sandvik L, et al. (2016) Impact of EMG changes in continuous vagal nerve monitoring in high-risk endocrine neck surgery. World J Surg 40: 672-680.

44. Randolph GW, Kamani D (2014) Intraoperative neural monitoring in thyroid cancer surgery. Langenbeck’s Archives of Surgery 399: 199-207.

45. Chandrasekhar SS, Randolph GW, Seidman MD, et al. (2013) Clinical practice guideline: Improving voice outcomes after thyroid surgery. Otolaryngol Head Neck Surg148: 51-53.

46. Musholt TJ, Clerici T, Dralle H, et al. (2011) German association of endocrine surgeons practice guidelines for the surgical treatment of benign thyroid disease. Langenbeck’s Arch Surg 396: 639-649.

47. Dionigi G, Frattini F (2013) Staged thyroidectomy: Time to consider intraoperative neuromonitoring as standard of care. Thyroid 23: 906-908.

48. Melin M, Schwarz K, Lammers BJ, et al. (2013) IONM-guided goiter surgery leading to two-stage thyroidectomy-indication and results. Langenbeck’s Arch Surg 398: 411-418.

49. Hermann M, Hellebart C, Freissmuth M (2004) Neuromonitoring in thyroid surgery: Prospective evaluation of intraoperative electrophysiological responses for the prediction of recurrent laryngeal nerve injury. Ann Surg 240: 639-649.

50. Kandil E, Mohsin K, Murcy MA, et al. (2018) Continuous vagal monitoring value in prevention of vocal cord paralysis following thyroid surgery. Laryngoscope 138: E1144-E1151.

51. Groves DA, Brown VJ (2005) Vagal nerve stimulation: A review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev 29: 493-500.

52. Schneider R, Randolph GW, Barczynski M, et al. (2016) Continuous intraoperative neural monitoring of the recurrent nerves in thyroid surgery: A quantum leap in technology. Gland surgery 5: 607-616.