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Review

Systematic review with meta-analysis of intraoperative neuromonitoring during thyroidectomy

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HIGHLIGHTS

- The meta-analysis and systematic review including latest and most literature about utilities of IONM in thyroid surgeries.
- The first systematic review with thyroid cancer focused discussion.
- First introduced comparison with CIONM and IIONM in meta-analysis.
- The most comprehensive discussion about RLNP reducing rate and Predictive Power.

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ABSTRACT

Introduction: Intraoperative neuromonitoring (IONM) has been a commonly used technology during thyroid surgery aimed at reducing the incidence of recurrent laryngeal nerve palsy (RLNP), which is a severe complication and leads to significant impacts on a patient's life. In order to give a comprehensive assessment for potential benefits and disadvantage of IONM, this meta-analysis and systematic review discusses RLNP rate, predictive power, continuous intraoperative neuromonitoring (CIONM), and emphasises application during thyroid cancer surgeries.

Methods: A literature search was performed in the following electronic databases: PubMed, Embase, and the Cochrane library from January 1, 2004 to July 30, 2016. After applying inclusion and exclusion criteria, 24 studies, including four prospective randomised trials, were selected. Heterogeneity of studies was checked by the Cochran Q test. Publication bias was assessed by funnel plots with Egger's linear regression test of asymmetry. Odds ratio (OR) was calculated by random effects model.

Results: Overall, 9203 patients and 17,203 nerves at risk (NAR) were included. Incidence of overall, transient, and persistent RLNP in IONM group were, respectively, 3.15%, 1.82%, and 0.67%, whereas for the ID group, they were 4.37%, 2.58%, and 1.07%. The summary OR of overall, transient, and persistent RLNP compared using IONM and ID were, respectively, 0.81 (95%CI 0.66–0.99), 0.76 (95%CI 0.61–0.94), and 0.78 (95%CI 0.55–1.09).

Conclusions: The presented data showed benefits of reducing RLNP rate by using IONM, but without statistical significance for persistent RLNP rate. For patients with thyroid cancer who undergo total thyroidectomy, using IONM may improve the outcome by reducing amount of residual thyroid tissue. However, no benefits were found for thyroid reoperation; visual identification and careful dissection remain standard for this challenging procedure. In addition, the relative low positive predictive power indicated intermittent intraoperative neuromonitoring (IIONM) may not be reliable; but CIONM was showed to be a more promising method, with prudent approach.

1. Introduction

With increasing numbers of thyroid surgery conducted in recent years, recurrent laryngeal nerve palsy (RLNP) has received more

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and more attention. Although the incidence of RLNP is relatively low, persistent hoarseness due to this condition has significant negative impact on a patient's quality of life [1]. In addition, RLNP has become the leading cause of litigation in a thyroidectomy [2]. Since being first introduced in 1966 as an adjunct to conventional visual identification of the RLNP during thyroid surgery [3], intraoperative neuromonitoring (IONM) has developed for 50 years. Although the use of IONM is widespread, and even considered to be the standard of care in some cancer centres, the effectiveness of this prevalent technology is still debatable.

The prevalence of using IONM during thyroidectomy is attributed to its two benefits: to verify the functional integrity of RLN during thyroid surgery, and to aid the surgeon in RLN localisation before visualisation during operations, especially for high-risk situations—reoperative settings and malignant disease surgery. The efficacy of the first purpose can be measured by predictive power (sensitivity, specificity, PPV, and NPV), and the utility of secondary purpose can be identified by reduction of RLNP's incidence (overall, transient, and persistent). It is critically important to develop a clearer understanding of the real impact of IONM. For this reason, the primary purpose of this study was to use the meta-analytic approach to assess the role of IONM in aiding thyroid surgery.

2. Methods

This systematic review was reported in accordance with the Primary Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [4] and the Cochrane Handbook for Systematic Reviews of Intervention. For performing the literature search, the following electronic databases were used: web-based PubMed database, Embase, and the Cochrane Library. Publication data were selected from January 1, 2004 to July 30, 2016. The following keywords and key terms with Boolean operators were used in electronic searching: thyroid, thyroidectomy, RLN, recurrent laryngeal nerve, IONM, intraoperative neuromonitoring, neuro, monitoring. Hand-searching of the reference list was performed in previously conducted meta-analysis and relevant articles.

2.1. Literature review

The exclusion criteria used in this study were the following: 1. No distinction between the results of the IONM group from the ID (control) group. 2. No specified value for number of nerves at risk (NAR) or patients. 3. No separate record of overall RLNP incidence by INOM versus visual identification alone; however, if only transient/persistent RLNP rate record was missed, the study was still eligible for inclusion. 4. The data were not collected by conducting head/neck surgeries. Two investigators, working independently, scanned and assessed the title, abstract, and full text; if the eligibility could not be determined from the title and abstract, of all searched studies against the inclusion and exclusion criteria. Any uncertainties and disagreements as to eligibility were referred to a third investigator and resolved by consensus. After obtaining the eligible publications, data were extracted into a predefined Excel table by one investigator and reviewed by another.

2.2. Data collection

The data items collected included the following: demographics characteristic of operations and patients, such as study type [i.e., prospective/retrospective comparative study (PCS/RCS), randomised controlled trial (RCT)]; country of study and dates; patients' average ages and genders; and the data for calculating primary outcome separately by with and without IONM: number of patients, number of nerves at risk (NAR), overall RLNP, transient RLNP, and persistent RLNP. Primary outcomes of interest were focusing on utility of IONM and predictive power of neuromonitoring technology. In order to assess the utility of using IONM, the incidence of overall, transient, and persistent RLNP was calculated between using IONM and visual identification alone. The predictive power of IONM was measured by sensitivity, specificity, and positive/negative predictive values.

2.3. Statistical analysis

Limited to the primary outcome of interest, risk of bias assessment was conducted for all included studies using the Cochrane Collaboration tool [5]. Specifically, assessments were made relative to: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, and (5) incomplete outcome data [6]. The data collected were analyzed using Stata statistical software. The Mantel–Haenszel method was used to calculate odds ratio (OR) and 95% confidence interval (CI). The Cochran Q test was used to test heterogeneity. Funnel plots with Egger's linear regression test of asymmetry were conducted for publication bias assessment in this systematic review.

3. Results

A flow chart of the literature selection process, including criteria for selected and excluded studies, is shown in Fig. 1. After being screened by authors independently, 24 studies were included in this systematic review [1,7–28], four of them are RCTs [10,15,20,28]. All of them were published in English from 2004 to 2016, and conducted in the US, Germany, China, France, Italy, Poland, Brazil, and Turkey (Table 1). In total, 9203 patients, with a median age of 47.5 years (range 21–68 years) and mean sex ratio of 7.3. Of this group, 4682 patients had IONM during thyroid surgery, and 4521 had visual identification alone and served as the control group. The total number of NAR was 17,203, of which 8668 were in the IONM group and 8535 were in the RLN control group. The overall RLNP rates were 3.15% ($n = 273$) with IONM and 4.37% ($n = 373$) in the control group. Transient RLNP rates were 1.82% ($n = 158$) for IONM and 2.58% ($n = 220$) in the control group. The persistent RLNP rates for IONM and ID were, respectively, 0.67% ($n = 58$) and 1.07% ($n = 91$). The present data, Table 2, showed reduced overall, transient, and persistent incidence of RLNP using IONM compared with using visual identification.

The summary OR of total RLN palsy, transient RLN palsy, and persistent RLN palsy for all included data for using IONM in comparison to visual identification alone on thyroidectomy in 24 studies, respectively, were 0.81 with 95% CI = 0.66 to 0.99, 0.76 with 95% CI = 0.61 to 0.94, and 0.78 with 95% CI = 0.55 to 1.09 (Figs. 2–4). The presented data demonstrated a statistically significant difference between using INOM and ID alone for decreasing overall and transient and RLN palsy rate. However, no significant difference was demonstrated for persistent RLNP rate between the two groups. The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous and could be combined. The funnel plots, shown in Figs. 2–4, indicate no influence of publication bias for total, transient, and persistent RLN palsy. There was lack of significant asymmetry in the funnel plot for all studies.

The analysis of RLNP incidence at thyroid cancer surgeries was conducted on 4 studies that reported the absolute numbers of RLNP considered at cancer surgeries [11,13,16,25]. The overall, transient and persistent RLNP rate, shown in Table 3, were 3.89%, 3.03% and 0.86% separately in IONM group compared with 6.58%, 5.02% and 1.57% in visual identification group. The differences were