Intraoperative Corticosteroids for Voice Outcomes among Patients Undergoing Thyroidectomy: A Systematic Review and Meta-analysis

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Abstract
Objective. To determine if a preoperative dose of intravenous corticosteroids reduces the risk of postoperative recurrent laryngeal nerve palsy and improves subjective voice outcomes among patients undergoing thyroidectomy.

Data Sources. PubMed, Cochrane database, and EMBASE.

Review Methods. Randomized controlled trials comparing corticosteroids with placebo on voice outcomes in thyroid surgery were extracted with standardized search criteria. Systematic review and meta-analysis were performed. With random effects models, trial data were pooled to determine the overall rate of recurrent laryngeal nerve palsy as well as secondary outcomes of adverse events, including wound infection and hyperglycemia.

Results. Four studies with a total of 517 patients met inclusion criteria. The overall rate of recurrent laryngeal nerve palsy was 5.78%. There was no difference in the rate of palsy between the corticosteroid and placebo groups (risk ratio, 0.70; 95% CI, 0.34-1.44). There was also no difference between the groups in regard to wound infection, healing, or hyperglycemia.

Conclusions. Preoperative corticosteroids do not appear to reduce the risk of recurrent laryngeal nerve palsy following thyroid surgery. There is insufficient evidence to assess its effect on subjective voice outcomes. More robust randomized controlled trials are needed to assess the effectiveness of perioperative steroids in improving voice outcomes after thyroidectomy.

Keywords
thyroidectomy, corticosteroids, voice, laryngeal nerves, hoarseness
The goal of this study was to determine if a preoperative dose of intravenous corticosteroids reduces the risk of postoperative recurrent laryngeal nerve palsy and improves subjective voice outcomes among patients undergoing thyroidectomy. Adverse events associated with intraoperative intravenous corticosteroids were also assessed.

Materials and Methods

Literature Search

Literature searches were performed in PubMed, Embase, and Cochrane databases to identify RCTs evaluating the effect of preoperative single-dose intravenous corticosteroids on voice outcomes among adult patients undergoing total or hemithyroidectomy. Search terms were developed by a medical librarian with extensive experience in performing literature searches for systematic reviews, in consultation with the research team. Search terms were adjusted for each electronic database and intentionally kept broad to include all possible studies. Due to wide variation in the definitions of study designs, the search strategy was not limited by study design type. The search strategy also was not limited to the English-language literature.

The following PubMed search terms were used: “thyroid diseases/surgery” [MeSH] and “voice disorders” [MeSH terms]. Embase terms included the following:

('endocrine surgery'/exp OR 'recurrent laryngeal nerve':ti,kw,de OR thyroidect*:ti,kw,de OR hemithyroidect*:ti,kw,de OR lobectomy*:ti,kw,de OR 'lung resection':de OR pneumonectomy*:ti,kw,de OR 'neck dissection':ti,kw,de) AND ('voice disorder'/exp OR 'vocal cord'/exp OR 'vocal cord':ti,kw OR 'voice'/exp OR voice:ti,kw,de OR dysphonia:ti,kw,de OR 'nerve palsy':ti,kw,de) AND ('steroid'/exp OR steroid*:ti,kw OR corticosteroid*:ti,kw OR glucocorticoid*:ti,kw OR deca dron:ti,kw OR dexamethasone*:ti,kw OR prednisolone*:ti,kw OR methylprednisolone*:ti,kw OR hydrocortisone*:ti,kw).

Finally, Cochrane search terms were as follows:

('recurrent laryngeal nerve’ OR thyroidect* OR hemithyroidect* OR lobectomy OR “lung resection” OR pneumonectomy* OR “neck dissection”) AND (voice OR “nerve palsy” OR “recurrent laryngeal nerve” OR dysphonia OR vocal cord).

The reference lists of key full-text articles included in the review were also checked to identify any potentially eligible studies.

Study Selection

Criteria for inclusion in the review were RCTs comparing intravenous corticosteroids given intraoperatively prior to skin incision against placebo or no treatment among adult patients undergoing thyroid surgery (total thyroidectomy or lobectomy). All studies identified with the search strategy were independently screened by 2 reviewers for inclusion in the review. Initially, a decision for potential inclusion was based on review of title and abstract. Where there was uncertainty about whether a study met the eligibility criteria, overcaution was applied, and the full article was obtained for detailed assessment against the inclusion criteria.

Based on this initial screen, assessment of full-text articles for potential inclusion was then performed independently and unblinded by 2 reviewers. The primary outcome of interest was the rate of postoperative recurrent laryngeal nerve palsy, while secondary measures included any subjective voice scores or outcomes and adverse events related to steroid use. Any articles not unanimously excluded or included were reexamined by both reviewers in concert until an outcome was agreed on.

Data Extraction and Analysis

Data extraction was performed independently by 3 reviewers, and disagreements were noted and resolved by consensus. Data were collected from each study via a data extraction form. The following information was collected: study design, inclusion criteria, intervention and control, and outcome measures (rates of recurrent laryngeal nerve palsy, subjective voice outcome measures, and adverse events). Attempts were made to contact authors of studies with incomplete data. The same review authors independently assessed risk of bias with the Cochrane risk-of-bias tool in Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark).

Statistical Analysis and Outcome Measurements

Meta-analysis was performed with Review Manager 5.3. Rates of recurrent laryngeal nerve palsy, continuous subjective voice outcome measures, and rates of adverse events were compared between groups. Heterogeneity was assessed with the I² statistic, which describes the percentage of variability in the effect estimates that can be attributed to heterogeneity rather than chance. Where applicable, meta-analysis with a random effects model was used to combine data. Due to diversity in included studies and variation in reported outcomes, where it was not appropriate to perform meta-analysis, included studies were combined in a narrative synthesis.

Results

A total of 758 manuscripts were compiled from the 3 literature searches described earlier. After removal of duplicates, 656 titles and abstracts were available for title and abstract review. Elimination of irrelevant studies yielded 19 articles that were reviewed in full text. Of these, 7 did not investigate the specific and independent effect of corticosteroids on voice and recurrent laryngeal nerve status; 4 were review articles or meta-analyses; and 4 lacked measurable voice outcomes. The remaining 4 studies were RCTs agreed on by the 3 reviewers to fulfill eligibility criteria and were ultimately included in the ensuing meta-analysis. The selection process is shown in Figure 1.
Narrative Synthesis

The 4 studies included in the analysis were RCTs. However, the protocols and outcomes in each varied widely. All trials compared the administration of 8 mg/2 mL of intravenous dexamethasone with an identical volume of saline given 30 to 90 minutes prior to incision. The risk-of-bias assessment is shown in Figure 2. One study had low risk of bias in all 7 measures examined; 2 had low risk in 6 measures; and 1 had low risk in 5 measures.

The study characteristics and outcomes are summarized in Table 1. Feroci et al performed an RCT of 104 patients undergoing thyroidectomy (total thyroidectomy or lobectomy) for benign disease. The primary outcome measure was postoperative nausea and vomiting, while the secondary outcome measures were pain and subjective voice disturbances. Subjective voice outcome was measured with a voice visual analog scale (VVAS), wherein a score of 100 indicated a normal voice and 0 the worst voice imaginable. One patient in the dexamethasone group was excluded from subjective voice function analysis due to recurrent laryngeal nerve injury. Sixty-nine patients completed the VVAS questionnaire at 8, 24, 32, and 48 hours after surgery. There were no significant differences in VVAS scores between the intervention and placebo groups. Unfortunately, no preoperative or baseline VVAS was reported, and attempts to contact the authors for this information were unsuccessful.

Nasiri et al randomized 68 patients to receive preoperative intravenous dexamethasone or placebo. A voice impairment score (VIS) questionnaire was completed by all 68 patients at 24 hours and 7 days after surgery. The VIS scores range from 0 to 40, with higher scores indicating worse voice outcomes. The intervention group had significantly lower VIS scores as compared with the placebo group on postoperative day 1. However, there was no difference between the groups on postoperative day 7.

Schietroma et al performed an RCT of 336 patients undergoing thyroidectomy. Vocal fold function was assessed by awake postoperative laryngoscopy. Eight patients (4 in each treatment group) were excluded from analysis for unknown reasons. In the remaining 328 patients, the rate of temporary recurrent laryngeal nerve palsy was higher in the placebo group (4.9%) versus the dexamethasone group (8.4%), and patients who had received preoperative dexamethasone experienced faster recovery of vocal fold function. There was no significant difference in the rate of permanent recurrent laryngeal nerve palsy.

Worni et al performed an RCT of 90 patients. Eighteen patients were excluded because of intraoperative-detected

Figure 1. PRISMA diagram.

Figure 2. Risk-of-bias summary.
malignancy and need for additional lymphadenectomy or because of protocol violations, leaving 72 patients for analysis. One patient in each arm had a transient recurrent laryngeal nerve palsy and was subsequently excluded from subjective voice analysis. Fifty-four patients completed the VVAS and Voice Handicap Index at postoperative 16, 24, 32, and 48 hours. There was no difference in Voice Handicap Index between the treated and placebo groups; however, a significant improvement in the VVAS was noted in the intervention group throughout the study period.

Meta-analysis

Information on rate of recurrent laryngeal nerve palsy could be obtained from 3 studies.4,5,9 Schietroma et al provided the number of patients with temporary and permanent recurrent laryngeal nerve palsy.9 Two other studies4,5 excluded patients with recurrent laryngeal nerve palsy from analysis of subjective voice outcomes. For the purpose of our analysis, these excluded patients were used to determine the rate of recurrent laryngeal nerve palsy for these 2 studies. The overall rate of recurrent laryngeal nerve palsy was 5.78%. Meta-analysis showed no difference in rates of recurrent laryngeal nerve palsy between the corticosteroid and placebo groups (Figure 3). Pooled trial data yielded a risk ratio of 0.70 (95% CI, 0.34-1.44; 3 studies, 502 participants, $I^2 = 0\%$).

Information on postoperative wound infection rates was available for all 4 studies. Three studies reported no wound infections in either group.4,5,8 Schietroma et al reported 4 cases of wound infection, 2 in each group (risk ratio, 1.01; 95% CI, 0.14-7.10).9 No cases of poor wound healing were noted in the 3 studies that reported on this outcome.4,5,8 No cases of hyperglycemia requiring medication were noted in the 1 study that reported on this outcome.8

Discussion

This study investigated the effect of a preoperative dose of intravenous corticosteroids on postoperative recurrent laryngeal nerve palsy rates and subjective voice outcomes among patients undergoing thyroidectomy. The overall results

Table 1. Characteristics of the Included Studies.a

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size, n</th>
<th>Patients</th>
<th>Outcome Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feroci et al (2011)</td>
<td>69</td>
<td>Adult patients undergoing thyroidectomy (total thyroidectomy or lobectomy)</td>
<td>VVAS</td>
<td>No difference in VVAS between groups. Note: baseline VVAS was not provided.</td>
</tr>
<tr>
<td>Nasir et al (2013)</td>
<td>68</td>
<td>Adult patients undergoing total thyroidectomy</td>
<td>VIS</td>
<td>Lower VIS in corticosteroid group on postoperative day 1. No difference on postoperative day 7.</td>
</tr>
<tr>
<td>Schietroma et al (2013)</td>
<td>328</td>
<td>Patients, age ≤75 y, undergoing thyroidectomy (total thyroidectomy or lobectomy)</td>
<td>Rates of RLN palsy</td>
<td>Lower rate of temporary RLN palsy and faster recovery of vocal fold function in corticosteroid group. No difference in rates of permanent RLN palsy</td>
</tr>
<tr>
<td>Worni et al (2008)</td>
<td>72</td>
<td>Adult patients undergoing thyroidectomy (total thyroidectomy or lobectomy)</td>
<td>VVAS and VHI</td>
<td>Improvement in VVAS in the corticosteroid group. No difference in VHI between groups</td>
</tr>
</tbody>
</table>

Abbreviations: RLN, recurrent laryngeal nerve; VHI, Voice Handicap Index; VIS, voice impairment score; VVAS, voice visual analog scale.

*aIntervention and control for each study: intravenous dexamethasone (8 mg/2 mL) vs saline (placebo).
indicate that preoperative corticosteroids do not reduce the risk of recurrent laryngeal nerve palsy. The effect of preoperative corticosteroids on subjective voice outcomes could not be assessed for several reasons: use of heterogeneous voice outcome measures, lack of baseline measures in 1 study, and the exclusion of patients with recurrent laryngeal nerve injury in several studies. Corticosteroids were not associated with higher rates of adverse events.

Recurrent laryngeal nerve palsy is one of the most feared complications of thyroid surgery. Identification and manipulation of the nerve often result in neuronal edema, and the presence of an intact nerve following dissection does not guarantee normal function. Although the incidence of permanent nerve dysfunction is rare, up to 80% of patients report temporary voice dysfunction following surgery. 

Other etiologies for voice disturbance may include superior laryngeal nerve injury, disruption of the strap muscles, laryngeal edema, or airway manipulation. Corticosteroids are potent inhibitors of inflammation, which may help minimize nerve damage. The use of steroids in facial paralysis secondary to Bell’s palsy has been well established. 

In traumatic facial nerve injuries, topical and systemic steroids were both shown to accelerate recovery in rodent models. The administration of methylprednisolone within 24 hours after traumatic optic neuropathy was also associated with improved visual acuity. Conversely, numerous studies showed corticosteroids to be ineffective in preventing neuronal injury or in hastening recovery among patients undergoing parotidectomy. 

The data addressing the efficacy of corticosteroids in recurrent laryngeal nerve protection during thyroid surgery are conflicting. Lore first reported a decrease in the incidence and duration of recurrent laryngeal nerve palsy among patients treated with perioperative corticosteroids. In their study cohort, the rate of temporary vocal fold paralysis was reduced from 9% to 2.6% and the length of vocal fold immobility from 9 to 2 months. Subsequent non-randomized studies, however, did not show a decreased risk of nerve dysfunction or a shortened duration of symptoms. 

In this meta-analysis of randomized clinical trials, pooled analysis revealed no observed difference in the overall rates of recurrent laryngeal nerve palsy between the corticosteroid and placebo groups. The study by Schietroma et al reported a decreased rate of temporary recurrent laryngeal nerve palsy and more rapid recovery in the corticosteroid groups but no difference in permanent recurrent laryngeal nerve palsy rates. Nasiri et al and Worni et al noted improved subjective voice outcomes among their patients receiving corticosteroids. However, improvement was not consistent across all outcome scales and was not sustained past postoperative 24 hours.

The strength of this current study lies in the increased statistical power resulting from the pooled analysis of level 1 evidence. However, this study has several limitations. Only 4 RCTs assessing the efficacy of preoperative dexamethasone in improving voice outcomes during thyroidec- tomy were available for analysis. Within these, there was significant heterogeneity in outcomes, which included subjective and objective measures reported at varying intervals that could not be analyzed in a pooled manner. Three studies had patient-reported voice outcomes; however, they used differing scales at variable postoperative intervals. Furthermore, 2 studies excluded patients with evidence of recurrent laryngeal nerve palsy from analysis of subjective voice outcomes. Prior work demonstrated that subjective voice evaluations do not necessarily correlate with visible laryngeal dysfunction. Only 1 study directly assessed recurrent laryngeal nerve palsy rates; however, recurrent laryngeal nerve palsy rates could be determined from the exclusion criteria in 2 other studies. These studies assessed recurrent laryngeal nerve function with laryngoscopy. It should be noted, however, that 1 study included in the analysis assessed recurrent laryngeal nerve function by direct laryngoscopy prior to extubation, which may have limited utility in evaluating vocal fold mobility. Finally, none of the included studies reported on power and sample size calculations for voice outcomes. 

In summary, this meta-analysis fails to support the efficacy of a single dose of preoperative corticosteroids in reducing the risk of recurrent laryngeal nerve palsy after thyroid surgery. The effect of preoperative corticosteroids on subjective voice outcome could not be determined due to use of heterogeneous voice outcome measures and poor study design. Corticosteroids were not associated with higher rates of adverse events.

Given its favorable safety profile and the potential to improve subjective voice outcomes, perioperative corticosteroids may be considered for patients undergoing thyroidec- tomy. However, well-designed RCTs are needed to further assess its efficacy in improving voice outcomes.

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Author Contributions

Julia E. Noel, data collection; data analysis and interpretation; manuscript preparation; final approval of the version to be published; agreement to be accountable for all aspects of the work; Maxwell P. Kligerman, data collection; data analysis and interpretation; manuscript preparation; final approval of the version to be published; agreement to be accountable for all aspects of the work; Uchechukwu C. Megwalu, study design and conduct; data collection; data analysis and interpretation; critical revision of manuscript; final approval of the version to be published; agreement to be accountable for all aspects of the work. Uchechukwu C. Megwalu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

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