Nimodipine Improves Vocal Fold and Facial Motion Recovery After Injury: A Systematic Review and Meta-Analysis

R. Jun Lin, MD, FRCSC, MSc; Michele Klein-Fedyshin, MSLS, BSN, RN, AHIP; Clark A. Rosen, MD, FACS

Nimodipine  可改善損傷後的聲帶與復原顏面動作功能：系統性回顧與統合分析

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commentary

顱神經損傷在耳鼻喉頭頸疾病中是常見的徵候，如顔面神經麻痺、耳鳴、眩暈、及聲帶麻痺等。除了肇因於疾病本身，醫源性的傷害亦時有所聞。在美觀及功能上的缺損外，嚴重時如雙側聲帶麻痺會影響呼吸道暢通，有危及生命之疑慮。但臨床上藥物治療其實效果不彰，所以醫界仍然在尋求對顱神經損傷的有效藥物治療。

Nimodipine 為一鈣離子通道阻斷劑，其適應症為高血壓治療與預防蛛蛛膜下出血後之血管痙攣。但此類鈣離子通道普遍存在於包含神經元在內的可激活細胞中，故有學者聯想此藥物是否亦有保護神經元的作用，因而有藥品仿單標示外使用 (off-label use) 的出現，但確實的機轉仍眾說紛紜。如小鼠的喉返神經損傷實驗中可改善神經再生與神經肌肉功能，可能是經由調控蘭式結 (nodes of Ranvier) 上的生長點的胞內鈣離子濃度，促進生長；而顔面神經損傷的研究則認為 nimodipine 可改善神經細胞的氧氣及養分供應，並降低胞內鈣離子濃度，減少細胞死亡，進一步可以抑制過度的神經再生或連帶運動產生。類似的效果也出現於聽覺與平衡功能改善的相關研究，顯示其對於噪音傷害的保護及前庭神經鞘瘤術後聽力保留有正面效益，甚至可改善耳鳴與眩暈。

綜觀上述，nimodipine 確實在 off-label use 的動物或臨床研究百家爭鳴，但缺乏大型客觀的研究。本文即嘗試以系統性回顧文獻的方法，利用統合分析，研究以 nimodipine 為單一治療藥物時，對於顱神經損傷的治療效果，並與安慰劑治療之群組比較。

本文使用 PRISMA 準則對常用的八大醫學資料庫做檢索，時間自 1987 年 1 月 1 日至 2017 年 10 月 11 日止，先導研究乃收集以 nimodipine 為單一藥物治療喉返神經，顔面神經及耳蝸前庭神經功能異常之相關文獻。喉返神經復原定義為麻痺進步至任何隨意動作；顔面神經復原定義為 House-Brackmann IV 至 IV 級進步至 I 至 III 級；耳蝸前庭神經功能復原則以文獻研究之症狀使用問卷評分是否改善。誤差風險 (risk of bias) 以 GRADE 工具評估。治療效果則以勝算比 (odds ratio) 評估。

前述文獻共 689 篇，經兩位本文作者獨立審核後，排除不符合變項，或資料不全等條件，最後有 9 篇納入研究。其中 3 篇為檢測耳蝸前庭神經之研究，包括 1 篇為主觀耳鳴量測，2 篇為眩暈嚴重度。3 篇研究喉返神經以語聲變為變項，而剩餘 3 篇研究顔面神經麻痹者則以顔面肌肉麻痹為變項。結果顯示總體而言顔神經以 nimodipine 為單一藥物治療勝算比為 6.09，95% 信賴區間 3.41, 10.87：異質性 (heterogeneity) 73%，顯示為顯著相關，中度變異性；但耳蝸前庭神經之研究則由於各研究變項之間變異性太大而無法列入統計。
聲帶麻痺的治療中，勝算比為 13.73，95% 信賴區間 6.21, 30.38；異質性 60%，顯示為顯著相關，中度變異性。而在顏面神經復原之統計，勝算比為 2.78，95% 信賴區間 1.20, 6.44；異質性 30%，顯示為顯著相關，低度變異性。此外值得注意的是，9 份文獻中有 5 份報告了藥物不良反應 (adverse events)，主要是低血壓引起的昏昏欲睡或昏眩，佔所有樣本數的 44.2%。原因可能與最大單次劑量與較長使用時間有關。誤差風險則因 5 篇為病例系列無法納入評估，顯示其統計品質評估仍有不足。

本文為第一篇發表的文獻，探討 nimodipine 單一藥物治療顱神經損傷之療效與安全性的系統性回顧與統合分析研究。現有證據顯示此藥對於聲帶與顏面麻痺的治療有正面的效果。但在未有大型隨機對照實驗的研究結果支持之前，對此類藥品仿單標示外使用方式仍建議不要視為常規。

關鍵字：Nimodipine, 顱神經損傷，藥品仿單標示外使用，聲帶麻痺，顏面麻痺，喉返神經，顏面神經，耳蝸前庭神經，勝算比，異質性，藥物不良反應。
Systematic Review

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**Introduction:** Nimodipine is a calcium channel blocker that has been used to treat hypertension and vasospasm. Emerging evidence in the literature suggests that it is neuroprotective by reducing cellular apoptosis after neuronal injury and promoting axonal sprouting at the nodes of Ranvier.

**Objectives:** To conduct a systematic review of the usage of nimodipine in cranial nerve injury and to perform a meta-analysis to estimate the efficacy of nimodipine on functional recovery of the injured cranial nerves.

**Methods:** Literature search was performed in eight databases using preferred reporting items for systematic reviews and meta analyses (PRISMA) guidelines. Human studies that used nimodipine as a monotherapy for treating cranial nerve injury were included for review. Cranial nerve function recovery was the primary outcome measure.

**Results:** 672 records were screened and 58 full texts in English were assessed. Nine studies were included in the final review. 5 of these, including 110 participants who received nimodipine for either recurrent laryngeal nerve or facial nerve injury and 556 controls, were used for meta-analysis. Nimodipine significantly increased the odds of vocal fold motion recovery (odds ratio [OR] 13.73, 95% confidence interval [CI] 6.21, 30.38, \( P < .01 \)) and the odds of facial motion recovery (OR 2.78, 95% CI 1.20, 6.44, \( P = .02 \)). Overall, nimodipine-treated patients had significantly higher odds of recovering vocal fold or facial motion compared with controls (OR 6.09, 95% CI 3.41, 10.87, \( P < .01 \)).

**Conclusion:** Existing evidence supports the positive effect of nimodipine on vocal fold and facial motion recovery after injury. Future research should focus on randomized clinical trials comparing recovery rates between nimodipine- and placebo-treated groups.

**Key Words:** Nimodipine, vocal cord paralysis, vocal fold paralysis, facial nerve injury, systematic review, meta-analysis.

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**INTRODUCTION**

Nimodipine is a calcium channel blocker that has been approved by the Food and Drug Administration for treatment of hypertension and reducing vasospasm after subarachnoid hemorrhage.\(^1\) Voltage-gated calcium channels are a group of ion-conducting pores located in the plasma membrane of excitable cells such as neurons.\(^2\) These have a selective permeability to calcium ions (Ca\(^{2+}\)). At resting membrane potential, these channels are typically closed, and the concentration of Ca\(^{2+}\) is much higher outside of the cell compared with the inside. In response to depolarization, the channels will open, which allows Ca\(^{2+}\) to enter the cell and result in various cellular responses, including neuron excitation.\(^3\) Nimodipine is highly lipophilic, which makes it rapidly cross the blood–brain barrier.\(^4\) Its main mechanism of action is to selectively block intracellular calcium ions influx through the L-type calcium channel blockers.

Various studies are available in the otolaryngology literature, suggesting that nimodipine exerts a neuroprotective effect on injured neurons. The exact mechanism remains unknown; however, there are many proposed theories. For recurrent laryngeal nerve (RLN) injury, nimodipine has been shown to improve nerve regeneration and neuromuscular function in rats.\(^4\) The mechanism of action is proposed to be increasing axonal growth by affecting the growth cones at the nodes of Ranvier, which is regulated by intracellular calcium levels.\(^5,6\) Clinically, off-label nimodipine therapy has been shown to improve recovery rate of purposeful vocal...
fold motion in patients with laryngeal electromyography (LEMG) proven significant RLN neuropathy from 20% to 60%.6 In facial nerve injury, it has been suggested that nimodipine may enhance supply of oxygen and nutrients to the injured neuronal cells and prevent intracellular accumulation of Ca2+, which reduces cell death.7 It also exerts a positive effect on the calcium levels in nerve growth cones to increase axonal sprouting.7 Further, nimodipine appears to suppress hyper-reinnervation, or synkinesis of the facial nerve, which is a dreaded complication after facial nerve injury, possibly through more rapid and functionally better reinnervation.8 Similarly for auditory and vestibular function, nimodipine has been suggested to help protect against acoustic trauma, preserve hearing post vestibular schwannoma surgery, and even improve tinnitus and vertigo.8–12

Although nimodipine has been utilized in numerous animal and clinical investigations beyond its approved indications, no large, multi-institutional clinical trials exist to investigate the efficacy of this pharmacotherapy for treatment of various cranial nerve injuries. The objective of the current study is to systematically review the literature and, when appropriate, perform a meta-analysis on the efficacy and safety of nimodipine as a monotherapy in the treatment of any cranial nerve injury. Specifically, we want to examine whether nimodipine monotherapy is more effective than placebo in recovering cranial nerve function in patients with cranial nerve injury/paralysis.

METHODS
This protocol-based systematic review and meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta analyses (PRISMA) guidelines (International Prospective Register of Systematic Reviews [PROSPERO] ID: CRD42016051857).13,14

Information Sources and Selection of Studies
A literature search was performed in eight databases, including PubMed, EMBASE, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials, Clinical Trials.gov, WHO International Clinical Trials Registry Platform, and the EU Clinical Trials Register from January 1, 1987, to October 11, 2017. Nimodipine was added as a search term as of 1987; therefore, citations after this date were retrieved. A health sciences librarian (M.K-F.) developed, piloted, and executed the searches. A preliminary search indicated that nimodipine was primarily used to treat RLN, facial nerve, and cochleovestibular nerve dysfunction; therefore, a formal literature search focused on these cranial nerves. The search strategy included medical subject headings (MeSH) as the following: (“Nimodipine”[MeSH] AND (“Facial Nerve”[MeSH] OR “Facial Nerve Injuries”[MeSH] OR “Facial Nerve Diseases”[MeSH]) OR “Facial Paralysis”[MeSH] OR “Vocal Cord Paralysis”[MeSH] OR “Recurrent Laryngeal Nerve” [MeSH] OR “Recurrent Laryngeal Nerve Injuries” [MeSH] OR “Cochlear Nerve”[MeSH] OR “Vestibulocochlear Nerve”[MeSH] OR “Hearing Loss, Sensorineural”[MeSH] OR “Hearing Disorders”[MeSH]). Searches excluded non-English-language articles.

Study Inclusion Criteria
Published clinical studies in humans including randomized controlled trials, cohort studies, case-controlled studies, and case series using nimodipine as a monotherapy for treatment of RLN, facial nerve, and cochleovestibular nerve injuries were included in the final review. Only studies using nimodipine as a monotherapy were included to avoid confounding from any add-on therapeutic agents to the interested outcome measures.

Study Exclusion Criteria
Investigations that used nimodipine as part of a combination therapy were excluded. Studies that investigated non-cranial nerve-related neuronal injuries (e.g., spinal cord injury, headaches) were excluded. Non-English articles, case reports, conference abstracts, letters and correspondence, expert opinion, and review articles were also excluded. Gray literature, such as government reports, policy statements, and conference proceedings, were not considered.

Study Selection and Data Extraction
Two authors (R.J.L. and C.A.R.) independently evaluated the titles and abstracts for inclusion eligibility. Reasons for exclusion were recorded and cross-checked for agreement. Disagreements were resolved by discussion and mutual consensus. Studies with similar participant...
<table>
<thead>
<tr>
<th>Source</th>
<th>Cranial Nerve Affected</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>No. of Patients in Intervention Group</th>
<th>No. of Patients in Control Group</th>
<th>Intervention (Nimodipine Monotherapy)</th>
<th>Control</th>
<th>Primary Outcome Measure</th>
<th>Study End Point</th>
<th>Adverse Events</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydman et al., 2009</td>
<td>RLN</td>
<td>Case-controlled study</td>
<td>1. NA</td>
<td>1. NA</td>
<td>60 mg PO TID × 12 weeks</td>
<td>No treatment</td>
<td>Any vocal fold motion recovery</td>
<td>6 months after RLN injury</td>
<td>Not described</td>
<td>All 3 patients in the intervention group recovered vocal fold motion, whereas only 2 patients from the control group recovered motion.</td>
<td></td>
</tr>
<tr>
<td>Rosen et al., 2014</td>
<td>RLN</td>
<td>Institutional historical case-controlled study</td>
<td>1. 56.8 ± 1.27</td>
<td>3 (30 vocal folds) 28 (30 vocal folds)</td>
<td>Start with 30 mg PO TID × 1 week, then increase to 60 mg PO TID × 12 weeks</td>
<td>No treatment</td>
<td>Any vocal fold motion recovery</td>
<td>3 months after RLN injury</td>
<td>3 dizziness, hypotension; 2 headaches; 1 chest heaviness; 1 urticaria; 1 joint swelling and facial flushing; 1 degree with exertion; 1 decreased BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sridharan et al., 2015</td>
<td>RLN</td>
<td>Case series</td>
<td>1. NA</td>
<td>23 296 (historical control data)</td>
<td>Start with 30 mg PO TID × 1 week, then increase to 60 mg PO TID × 12 weeks</td>
<td>NA</td>
<td>Any vocal fold motion recovery</td>
<td>3 months after RLN injury</td>
<td>Not described</td>
<td>18 of 30 recovered vocal fold motion in the intervention group, and 5 of 25 recovered motion in the historical control group.</td>
<td></td>
</tr>
<tr>
<td>Kunert et al., 2016</td>
<td>Facial nerve</td>
<td>Case-controlled study</td>
<td>1. NA</td>
<td>47 160</td>
<td>60 mg PO QID × 10 days</td>
<td>No treatment</td>
<td>Facial motion recovery from HB IV–I</td>
<td>6 months after facial nerve injury</td>
<td>Not described</td>
<td>41 of 55 (75%) in the intervention group recovered facial motion, whereas 123 of 165 (74%) in the control group recovered motion.</td>
<td></td>
</tr>
<tr>
<td>Scheller et al., 2012</td>
<td>Facial nerve</td>
<td>Case series</td>
<td>1. 38.21 ± 15.5</td>
<td>12 35</td>
<td>60 mg PO 6 times daily × 8 weeks</td>
<td>NA</td>
<td>Facial motion recovery from HB IV–I</td>
<td>2 months after initiation of intervention</td>
<td>1 hypotension</td>
<td>All 11 patients recovered facial motion to HB I-I.</td>
<td></td>
</tr>
<tr>
<td>Scheller et al., 2014</td>
<td>Facial nerve</td>
<td>Case series</td>
<td>1. Median age 52 (25-86)</td>
<td>17 89</td>
<td>60 mg PO 6 times daily × 8 days</td>
<td>NA</td>
<td>Facial motion recovery from HB IV–I</td>
<td>12 months after vestibular schwannoma surgery</td>
<td>No adverse events</td>
<td>3 of 7 patients recovered facial motion to HB I-I.</td>
<td></td>
</tr>
<tr>
<td>Davies et al., 1994</td>
<td>Cochleovestibular nerve (limbic)</td>
<td>Case series</td>
<td>1. NA</td>
<td>31 NA</td>
<td>30 mg PO QID × 4 weeks</td>
<td>NA</td>
<td>Subjective tinnitus</td>
<td>At completion of nimodipine treatment</td>
<td>Not described</td>
<td>17 of 31 reported no change; 6/31 reported improvement; 8/31 reported worsening tinnitus</td>
<td></td>
</tr>
<tr>
<td>Liddell et al., 2013</td>
<td>Cochleovestibular nerve (vertigo)</td>
<td>RCT</td>
<td>1. 46.7 ± 13.3</td>
<td>51 NA</td>
<td>90 mg PO once daily × 8 weeks</td>
<td>Nimodipine 30 mg PO TID × 8 weeks</td>
<td>At least a 50% reduction in vertigo</td>
<td>At least a 50% reduction in vertigo</td>
<td>1 dizziness, 1 diplopia, 1 headache, 2 dizziness, 1 vertigo, 1 diplopia, 1 headache</td>
<td>92% had at least 50% reduction in vertigo. Severity in both nimodipine dosing regimens were comparable.</td>
<td></td>
</tr>
<tr>
<td>Raneve et al., 2002</td>
<td>Cochleovestibular nerve (vertigo)</td>
<td>RCT</td>
<td>1. NA</td>
<td>89 92</td>
<td>90 mg PO once daily × 8 weeks</td>
<td>Nimodipine 100 mg PO once daily × 4 weeks</td>
<td>Subjective report of vertigo</td>
<td>14 weeks after initiation of treatment</td>
<td>66 of 88 (74.6%) reported at least 1 adverse event, including headache, altered HP function tests, weight gain, and membranous 3 serious adverse events were reported, including subaxial fracture, unstable angina, and dizziness.</td>
<td>Incidence of moderate and severe vertigo decreased (p &lt; 0.001) by ~76% and ~65% in the nimodipine group. Incidence of mild, moderate, and severe vertigo decreased by ~53.2%, ~56.8%, and ~49.8%, respectively, in the nimodipine group. There was no between-group difference except for mild vertigo. (P = 0.92).</td>
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</table>

BP = blood pressure; HB = House-Brackmann scale; NA = not available; PO = per oral; QID = four times a day; RCT = randomized controlled trial; RLN = recurrent laryngeal nerve; TID = three times a day.
population, methodology, and outcome measures were included in the meta-analysis. Data were independently extracted by the same two investigators (R.J.L. and C.A.R.) using structured, customized forms from each included study. Every effort was made to contact the original study author when data clarification or additional data was required.

The following data were extracted: study country of origin, cranial nerve investigated, treatment and control group sizes, nimodipine and comparator dosing regimen, route and duration of drug administration, definition of outcome measures, adverse events, and follow-up duration.

**Definition of Outcome Measures**

The primary outcome measure of the review was cranial nerve functional recovery. In the case of vocal fold paralysis secondary to RLN injury, this was defined as recovery of any purposeful vocal fold motion.\(^\text{15}\) In cases of facial nerve paralysis, this was defined as recovery from House-Brackmann (HB) grade IV to VI injury (moderately severe to total paralysis) to HB grade I to III (normal to moderate paralysis). For cochleovestibular dysfunction, the primary outcome depended on the primary otologic symptom the study was investigating. For example, subjective tinnitus rating would be the primary outcome measure in a study that was investigating tinnitus, whereas Vertigo Severity Index would be in those that were examining peripheral vertigo. Secondary outcome measure included any adverse events reported with nimodipine monotherapy.

**Risk of Bias Assessment**

Risk of bias was assessed by author R.J.L. Quality assessment of randomized controlled trials were rated using the Cochrane grading of recommendations assessment, development and evaluation (GRADE) tool,\(^\text{16}\) whereas quality assessment of cohort studies and case-controlled studies were rated using the respective Newcastle-Ottawa Scale.\(^\text{17}\) Whenever possible, studies of similar risk of bias were pooled in the meta-analysis. Publication bias was assessed using a funnel plot.

**Data Synthesis**

A narrative synthesis was conducted for all included studies. Studies with comparable baseline characteristics between intervention and controls groups, interventions regarding nimodipine dosage and route of administration, and outcome measures as well as risk of bias were selected for meta-analysis. Given the heterogeneity across trials, a random effects model was constructed using RevMan version 5.0 (Cochrane Collaboration). All significant tests were 2-tailed, with \(P < .05\) considered statistically significant. The proportion of variability in point estimates attributable to between-study heterogeneity was quantified by the \(I^2\) statistic and interpreted qualitatively as low (25%–50%), moderate (50%–75%), and high (75%–100%).\(^\text{18}\)

Odds ratios (ORs) were used as the treatment effect for cranial nerve functional recovery. When control data were not available in the original report, every effort was made to contact the authors to retrieve the study raw data. Historical control data were obtained from studies with similar patient populations if the raw control data were not available. Subgroup analysis was conducted based on different cranial nerve injuries.

**RESULTS**

**Study Selection and Characteristics**

Searches identified 672 records. After removal of 183 duplicates, 489 unique records were identified, of which 58 were potentially relevant based on initial title and abstract screening (Fig. 1). 9 articles were included in the final systematic review: Of these 9 studies, 3 examined cochleovestibular nerve function, including 1 study investigating subjective tinnitus and 2 studies examining vertigo severity.\(^\text{11,12,19}\) 3 studies investigated RLN injury as represented by vocal fold paralysis\(^\text{4,6,20}\) and the remaining 3 articles studied facial nerve injury as represented by facial muscle paralysis.\(^\text{21–23}\) Study characteristics including study design, number of subjects, intervention, comparison, primary outcome measure, follow-up duration, adverse events, and summary of results were tabulated in Table I.

**Synthesis of Results**

Overall, nimodipine-treated patients had significantly higher odds of recovering vocal fold or facial motion compared with controls (OR 6.09; 95% CI 3.41, 10.87; \(P < .01\); heterogeneity, \(I^2 = 73\%\)) (Fig. 2). We were not able to combine data from studies investigating the cochleovestibular nerve given their heterogeneity. Subgroup analyses based on cranial nerve of interest were discussed below.

**EFFECT OF NIMODIPINE ON VOCAL FOLD MOTION RECOVERY.** The efficacy of nimodipine on vocal fold motion recovery following RLN injury was assessed in three studies (Table I).\(^\text{4,6,20}\) Of the three studies, two were of a case-controlled design, both of which scored 6 out of 9 asterisks on the Newcastle-Ottawa Scale, indicating fair quality. For Rosen et al., institutional historical control data were used as a comparison group, and these data were reported previously in a separate study.\(^\text{24}\) The third study was a case series without a comparison group.\(^\text{20}\) We were able to find a meta-analysis on the natural recovery rate of vocal fold motion in patients with poor prognosis of vocal fold motion recovery based on LEMG criteria and used these data as a comparison group for the third study.\(^\text{25}\) Hence, data from all three studies could be combined for meta-analysis (56 participants who received nimodipine and 325 controls). This showed nimodipine treatment was associated with a significant increase in odds of vocal fold motion recovery at 3 to 6 months after RLN injury (OR, 13.73; 95% confidence interval [CI] 6.21, 30.38; heterogeneity, \(I^2 = 60\%\)). This was statistically significant (\(P < .01\)) (Fig. 2). \(I^2\) statistic was 60%, indicating moderate heterogeneity among the studies.
EFFECT OF NIMODIPINE ON FACIAL MOTION RECOVERY. The efficacy of nimodipine on facial motion recovery following facial nerve injury was assessed in three studies (Table I). Of the three studies, one was a case-controlled study investigating facial nerve function after vestibular schwannoma surgery. This study scored 6 out of 9 stars on the Newcastle-Ottawa Scale, indicating fair quality. The remaining two studies were case series. Scheller et al. 2012 studied facial nerve paralysis post maxillofacial surgery, not vestibular schwannoma surgery. Hence, this study was not included in the meta-analysis. In Scheller et al. 2014, enteral administration was compared to parenteral administration of nimodipine. There was no placebo group. For comparability with other included studies, only data from the enteral nimodipine arm were included in the meta-analysis. We found a previous report on the natural recovery rate of facial motion in a comparable patient population after vestibular schwannoma resection and used these data as a comparison group for Scheller et al. 2014. Therefore, data from Kunert et al. and Scheller et al. 2014 were combined for meta-analysis (54 participants who received nimodipine and 231 controls). This showed nimodipine treatment was associated with a moderate increase in odds of facial motion recovery at 6 to 12 months after vestibular schwannoma surgery (OR, 2.78; 95% CI 1.20, 6.44; heterogeneity, $I^2 = 30\%$). This was statistically significant ($P = .02$) (Fig. 2). $I^2$ statistic was 30%, indicating low heterogeneity among the studies.

EFFECT OF NIMODIPINE ON TINNITUS AND VERTIGO. Three trials investigated the effect of nimodipine on symptoms relating to the cochleovestibular nerve (Table I). One trial of 31 participants investigated subjective tinnitus using a case series design. Subjective tinnitus rating was the primary outcome measure. Two trials investigated vertigo. Pianese et al. was a randomized design comparing nimodipine to another calcium channel blocker cinnarizine, and subjective report of vertigo was the outcome measure. Lisbeth et al. was also a randomized trial of two different formulation of oral nimodipine (90 mg once daily vs. 30 mg 3 times daily). No placebo control arm was included. A 50% reduction in Vertigo Severity Index was used as the primary outcome measure. These studies showed general improvement of patient-reported symptoms of subjective tinnitus and vertigo; however, the study methodology and outcome measures were too heterogeneous to be combined for meta-analysis. Safety data on nimodipine from these studies were included in the analysis of the secondary outcome. Summary of results of these studies were presented in Table I.

Adverse Events Associated With Nimodipine Monotherapy

Of the nine included studies, five reported on adverse events associated with nimodipine treatment (Table I), the most common of which was drowsiness and dizziness likely secondary to...
### TABLE II.
Risk of Bias Assessment in Included Studies Using Randomized Controlled or Case-Controlled Designs.

<table>
<thead>
<tr>
<th>Source</th>
<th>Cranial Nerve of Interest</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessors</th>
<th>Incomplete outcome data</th>
<th>Select outcome reporting</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisbeth et al., 2013</td>
<td>Cochleovestibular nerve (vertigo)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Pianese et al., 2002</td>
<td>Cochleovestibular nerve (vertigo)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

#### Newcastle-Ottawa Scale for Case-Controlled Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Cranial Nerve of Interest</th>
<th>Selection</th>
<th>Comparability</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydman et al., 2009</td>
<td>Recurrent laryngeal nerve paralysis</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Rosen et al., 2014</td>
<td>Recurrent laryngeal nerve paralysis</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Kunert et al., 2016</td>
<td>Facial nerve paralysis</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Scheller et al., 2014</td>
<td>Facial nerve paralysis</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

#### Notes:
- Quality of randomized controlled trials was assessed using the Cochrane GRADE tool. Quality of case-controlled trials was assessed using the Newcastle-Ottawa Scale for Case-Controlled Studies. Quality of case series was not assessed because there was no standard quality assessment tools available for this type of studies.
- The remaining included studies, including Davies et al., Scheller et al., 2012, and Sridharan et al., were case series.
- Cochrane GRADE tool for Randomized Controlled Trials: This tool assessed study quality based on 6 domains, including selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. Each domain was rated as low, high, or unclear risk of bias.
- Newcastle-Ottawa Scale for Case-Controlled Studies: This scale has a scoring system using asterisks based on 3 domains, including selection of study groups, comparability of groups, and ascertainment of exposure. A maximum of 4 asterisks could be given to the selection domain, 2 asterisks to the comparability domain, and 3 asterisks to the exposure domain. A greater number of asterisks indicated higher quality.
hypotension. In total, 87 of 197 (44.2%) participants experienced adverse effects. This data was skewed by the following two studies. Scheller et al. 2014 reported zero adverse events.23 In Pianese et al., 66 of 89 (58.4%) participants reported at least one adverse event.12 If we excluded Scheller et al. 2014 and Pianese et al. as outliers, the overall adverse event rate was 16 out of 91 (17.6%).

**Risk of Bias Within Studies**

Summary of risk of bias assessment was presented in Table II. Currently, there is no standard quality assessment tool for case series; hence, these studies did not have a risk of bias assessment.

Two randomized controlled studies were assessed by the Cochrane GRADE tool.12,19 Neither study clearly indicated how random sequence was generated, how the allocation assignment was concealed from the investigators, or whether the outcome assessors were blinded to participant allocation to prevent bias. Lisbeth et al. had a very high attrition rate from both arms of the study, but no explanations were provided as to why this occurred, putting the study at a high risk for incomplete outcome data.19 Pianese et al. had different dosing frequencies in the intervention and the control arms, therefore making blinding impossible for the participants and study personnel.12

For the included case-controlled studies, all scored 6 out of 9 on the Newcastle-Ottawa Scale, indicating fair quality. All scored four asterisks in the patient selection domain. Under comparability, none of the studies controlled for confounders such as age, sex, and comorbidities; therefore, only one out of two asterisks was scored. Under the outcome subscale, none of the studies reported on the nonresponse rate in the intervention group as well as the control group.

**Publication Bias**

A funnel plot for publication bias was generated using the five studies included in the meta-analysis (Fig. 3).4,6,20,21,23 The plot displayed the relationship between study size and effect size. The y-axis represented the standard error, whereas the x-axis represented effect size in the form of OR. The plot showed clustering of studies near the top of the funnel, and only one study at the bottom of the funnel, indicating moderate publication bias. However, these results needed to be interpreted with caution because there were only a limited number of studies included in the analysis.

**DISCUSSION**

**Nimodipine for Vocal Fold and Facial Paralysis**

Nimodipine monotherapy results in a six times higher odds of recovering vocal fold and facial motion post injury compared with controls. Specifically, the odds of motion recovery was 13.73 times higher in vocal fold paralysis at 3 to 6 months after RLN injury and 2.78 times higher in facial paralysis at 6 to 12 months following vestibular schwannoma resection. Studies on cochleovestibular symptoms such as tinnitus and vertigo were too heterogeneous to draw any conclusions. Other cranial nerves were not in the review either because there were no studies investigating the nerve in question or they did not fit the study inclusion criteria. The dosing regimen in the treatment of vocal fold paralysis was consistent across studies at 60 mg orally three times daily for 12 weeks.4,6,20 For the treatment of facial nerve paralysis, the dosage was typically 60 mg; however, the frequency of dosing as well as the duration of treatment varied among the three included studies.21–23

In the case of vocal fold paralysis secondary to RLN injury, motion was completely absent to begin with, and we were interested in recovery of any purposeful vocal fold motion following nimodipine therapy.15 In cases of facial nerve paralysis, the outcome measure was defined as facial motion recovery from HB grade IV to VI (moderate–severe–total paralysis) to HB grade I to III (normal–moderate paralysis). This could also be considered as recovery of any facial motion following injury. HB grade III was chosen as the cutoff because these patients do not have disfiguring differences between the two sides at rest, and eye closure is complete with effort. After defining the outcomes, we were able to synthesize eligible studies into a meta-analysis and performed a subgroup analysis based on the cranial nerve in question. As a result, heterogeneity of included studies was either moderate (vocal fold paralysis) or low (facial paralysis).

Preclinical animal studies also supported the use of nimodipine in vocal fold and facial paralysis. In a rat study of RLN crush injury, compound muscle action potential (CMAP) in the posterior cricoarytenoid (PCA) muscle and PCA neuron counts in nimodipine-treated animals were compared with placebo and sham-surgery groups.27 At 6 weeks following RLN injury, CMAP in the nimodipine group appeared similar in shape to that of sham-operated animals, and the amplitudes were significantly higher compared to placebo. Additionally, the
number of neurons that had reinnervated the PCA was significantly higher in the nimodipine group compared with the placebo group. Similarly, in a rat study involving unilateral transection and re-anastomosis of facial nerve, neuron count was performed by retrograde labeling of facial motor neurons that projected into the mimetic muscles of the rat whisker pad.26 In the early days post injury, that was, between day 14 to 28 following facial nerve transection, the nimodipine-treated group persistently had significantly higher number of regenerated facial motor neurons compared with placebo animals. After 56 days from the onset of injury, nimodipine-treated animals had been shown to suppress hyperinnervation compared with placebo. This was postulated to occur through more rapid and functionally better reinnervation. Prevention of hyperinnervation is very important clinically because this is thought to prevent facial nerve synkinesis, or abnormal synchronization of facial movement. Although the exact mechanism is unclear, nimodipine has been hypothesized to exert a dual effect on neurons through these animal studies. Nimodipine crosses the blood–brain barrier and binds to specific dihydropyridine receptors that in turn prevent calcium influx into the injured neuronal cell bodies.28 Secondly, it regulates intracellular calcium in outgrowing neuronal sprouts and reduces intracellular accumulation of calcium that could lead to apoptosis in injured neurons.27–30 In summary, the remarkable efficacy results from the current review and meta-analysis are further supported by animal data.27–30

Quality Assessment and Publication Bias
The quality of the included clinical studies is not of the highest quality. Most studies were case series or case-controlled studies with a very small sample size. For studies without control data, historical control data were obtained for comparison. Usage of historical control data has several limitations. The groups may have potential differences due to a separation in time, such as differences in diagnostic criteria and management over time. Studies from which the control data are derived may have different definitions regarding outcomes and covariates of their subjects. Further, there may be data quality issues such as missing data in historical records. However, historical control studies chosen to be included in the current meta-analysis were vetted, such that the patient population, methods of assessment, and outcome measures were sufficiently similar to those in the intervention studies in order to minimize bias. This led to increased power and reduced type I error, as well as comparison of treatment effects between the intervention and control groups.

In the absence of publication bias, the studies will be distributed symmetrically about the mean effect size because sampling error is random. In the presence of publication bias, the studies are expected to show symmetry at the top, a few studies missing in the middle, and more studies missing near the bottom on the funnel plot. Publication bias due to smaller studies without statistically significant results not being published will result in an asymmetrical funnel plot with a visible gap. Overall, there is an asymmetry of the study distribution suggesting publication bias (Fig. 3). The direction of effect is toward the right, and a gap is seen on the left near the bottom of the plot, indicating where nonsignificant studies would have been if they had been published. However, these results need to be interpreted with caution because there are only a limited number of studies included in the analysis.

Adverse Events
Adverse events were not systematically examined in all studies. Any possible patient-related risk factors that could lead to the development of adverse events such as age, sex, or comorbidities were not investigated. Rosen et al. reported on seven incidents of adverse events within the first two weeks of therapy initiation, which resulted in therapy cessation.6 An additional three adverse events were reported at conclusion of nimodipine therapy, which did not result in discontinuation of therapy. Scheller et al. 2012 reported one incident of hypotonia that resulted in study dropout.22 However, no serious adverse events were reported. Lisbeth et al. reported five adverse events resulting in no treatment suspension.19 Scheller et al. 2014 reported zero adverse events.23 Zero events in studies require careful interpretation because the lack of reported harms may have different reasons: they may not have occurred; they may not have been investigated; or they may have been detected but not reported.31 Finally, Pianese et al. reported the highest proportion of participants experiencing adverse events (58.4%).12 Three serious adverse events were reported, including cuboid fracture, unstable angina, and serious dizziness. However, only the participant with serious dizziness prematurely discontinued the study. This study used 90 mg of nimodipine orally once a day for 15 weeks. This was not the highest daily dosing regimen among the included studies. However, it had the highest one-time dose and the longest treatment duration, which might have contributed to the high adverse event rate. This study also had the most systematic approach of evaluating nimodipine safety. All participants underwent a complete physical exam and laboratory evaluation including blood count, kidney function tests, liver function tests, and a pregnancy test prior to therapy initiation. Nimodipine was not administered to those who were found to have hepatic or renal dysfunction. In addition, all participants were evaluated every 4 weeks to detect adverse events. Although the reported adverse event rate was very high in this study, it was comparable to its comparator group using cinnarizine, an antihistamine medication and also a calcium channel inhibitor. In total, 44.2% of study participants experienced adverse effects. If we excluded Scheller et al. 2014 and Pianese et al. as outliers, the overall adverse event rate was 16 out of 91 (17.6%). Future investigations are needed to systematically examine and document adverse events associated with nimodipine monotherapy at a commonly prescribed dose and treatment duration.
CONCLUSION

Implications for Clinicians and Future Directions

The current systematic review and meta-analysis is the first to examine the efficacy and safety of nimodipine monotherapy for cranial nerve injury. Nimodipine has been shown to be a promising medical therapy in the treatment of vocal fold and facial paralysis by existing evidence. However, it should not be used on a routine basis for these off-label indications given the current level of evidence. There are no large randomized clinical trials conducted to date, and many studies vary in nimodipine dosing regimen, treatment duration, and follow-up period. To address these issues, collaboration among otolaryngologists is needed to implement a large multi-center clinical trial to investigate nimodipine monotherapy as a medical treatment for either vocal fold paralysis or facial paralysis. Clear patient inclusion criteria and a specific dosing scheme needs to be established. Further, side-effect profile of this medication needs to be methodically documented. We hope that with stronger evidence, nimodipine can be added to the armamentarium of treatment of cranial nerve injuries in the future.

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BIBLIOGRAPHY