Outcome With Immediate Direct Anastomosis of Recurrent Laryngeal Nerves Injured During Thyroidectomy

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Objectives/Hypothesis: Management of unrecognized recurrent laryngeal nerve injury typically entails delayed phonosurgical intervention and laryngeal reinnervation, but in cases of recognized injury, nerve anastomosis has been considered standard management. However, the well-organized outcome analysis of nerve anastomosis has been insufficient. We performed immediate direct anastomosis of recurrent laryngeal nerves injured during surgery for thyroid cancer, and subsequent patient outcomes were analyzed.

Study Design: A total 14 patients sustaining recurrent laryngeal nerve injury during thyroidectomy were recruited for the study. Patients undergoing immediate direct reparative anastomosis of the injured nerves constituted the test group, whereas the controls of group 2 (n = 4) did not.

Methods: At follow-up, all patients submitted to rigid laryngoscopy at 3, 6, and 12 months postoperatively. Subjective and objective outcomes of the two groups were then compared.

Results: At 12 months postoperatively, group 1 showed greater improvement in maximum phonation time, glottic gap scores, GRBAS (grade, roughness, breathiness, asthenia, and strain) scales, aspiration scoring, and Voice Handicap Index than controls of group 2. Moreover, group 1 showed an improvement in all five categories at 12 months postoperatively, compared with status at 3 months. None of the patients in group 1 showed laryngoscopic evidence of vocal cord atrophy.

Conclusion: In this study, patients undergoing immediate direct recurrent laryngeal nerve anastomosis demonstrated better phonation and perceptually rated voice quality than those who did not undergo repair.

Key Words: Injured recurrent laryngeal nerve, immediate nerve anastomosis, direct nerve anastomosis.

Level of Evidence: 3b.

INTRODUCTION

Recurrent laryngeal nerve (RLN) paralysis is the most common and significant complication of thyroid or parathyroid cancer surgery.1 Unilateral RLN paralysis is often due to the adhesions that accompany thyroid cancer.2 Even with no signs of paralysis preoperatively, a cancerous thyroid gland may be found firmly adherent to RLN intraoperatively, in which case a segment of RLN must be sacrificed for the sake of cancer eradication.2 In addition to problematic adhesions, iatrogenic injuries, such as a transection, clamping, stretching, electrothermal injury, ligature entrapment, or ischemia may result in RLN paralysis.1 Unilateral loss of vocal fold innervation culminates in the loss of motion, flaccidity of the paralyzed fold, and subsequent atrophy of laryngeal muscle. A height disparity between paralytic and intact mobile folds may likewise ensue.3 Consequently, incomplete glottal closure and vocal fold motion impairment4 may then be manifested as hoarseness, shortened phonation, and aspiration.5,6

Postthyroidectomy patients with RLN palsy, who do not have recognized RLN injury intraoperatively, are generally managed conservatively. After several months of postsurgical observation, only patients who desire vocal improvement may opt for a phonosurgical procedure.7 Such interventions include type I thyroplasty,8 arytenoid adduction,9 and vocal cord injection.10–12 Breathy hoarseness and voice quality may improve thereafter,2 although atrophy of laryngeal muscle or vocal cord are not prevented7 and long-term benefits of these procedures are inconsistent.13,14 Surgical reinnervation has proved effective in restoring neural function to laryngeal muscles, thus preventing atrophy, improving the bulk and position of vocal folds,5,13 and enhancing overall vocal quality.15

On the other hand, when the RLN injury is recognized, immediate direct nerve anastomosis is the standard
treatment. However, well-organized outcome analysis of nerve anastomosis has been insufficient because it is difficult to obtain a control group. We therefore compared patients with immediate direct RLN anastomosis to patients without nerve anastomosis in spite of recognized nerve injury.

PATIENTS AND METHODS

Between 2004 and 2011, 8,241 patients undergoing total or subtotal thyroidectomy for thyroid cancer at Gangnam Severance Hospital were reviewed retrospectively. Among these patients, 14 (14/8,241, 0.17%) had suffered therapeutic sacrifice (n = 10) or iatrogenic transection (n = 4) of RLN. Immediate, direct RLN anastomosis was conducted if resected nerve segments were <5 mm and/or the severed ends of RLN could be approximated without tension. Anastomosis (group 1; n = 10) entailed an end-to-end epineural repair with sutures (3–7; mean, 4.3) using 7-0 to 9-0 Ethilon (Ethicon Inc, Somerville, NJ) (Table I). Patients of group 2 (n = 4) did not undergo RLN repair (Table II). Mean postoperative follow-up times were 19.6 months (range, 14–27 months) and 19.3 months (range 14–23 months) for groups 1 and 2, respectively. None of the 14 patients were irradiated, and all were examined at 3, 6, and 12 months postoperatively. If vocal cord medialization was needed for atrophy or increased glottal gap (by 70-degree rigid laryngoscopy), injection laryngoplasty was performed using Restylane (Medicis Aesthetic Inc, AZ) or Artesnese (Middleton Cosmetic Corp, Toronto, Ontario, Canada) filler (0.3–0.5 cc; mean, 0.5 cc). This procedure was routinely performed for each patient 2 to 6 months postoperatively (mean, 3.5 months).

Outcome Analysis: Objective and Subjective Assessment

Outcomes of anastomosis were analyzed by objective and subjective means. For objective assessment, maximum phonation time (MPT), measuring sustained “a” vowel phonation at comfortable pitch and loudness, served as one index. In addition, the relative magnitude of glottal gap was scored on a 5-point scale6 (by 70-degree rigid laryngoscopy) by three trained laryngologists (Table III and Fig 1), who also rated perceived voice quality according to the grade, roughness, breathiness, asthenia, and strain (GRBAS) scales.6 This was gauged by a 5-point scale as follows: normal (0), mild dysphonia (1), moderate dysphonia (2), severe dysphonia (3), and aphony (4).6 Patients were scored sustained “I” and “a” phonation by the GRBAS scale, but all other patient-generated assessments were subjective in nature. Aspiration was rated on 4-point scale of none (0), mild (1), moderate (2), or severe (3). In this regard, “mild” applied to occasional choking, without a need for dietary modifications (as reported by patients); whereas “moderate” constituted occasional choking, requiring dietary adjustment; and “severe” corresponded with obligatory feeding tube placement for alimentation.6 Physicians filled out the score according to patient’s report.

The Voice Handicap Index (VHI), incorporating functional, physical, and emotional categories, gave individual patients a chance to rate their own voice quality, as perceived.17 Each 10-question category (total of 30 questions) calls for scored responses of “never” (0), “almost never” (1), “sometimes” (2), “almost always” (3), or “always” (4). All 30 responses were summed for a total VHI score of 0 to 120, with 0 as normal voice (Table IV).

Statistical Analysis

To compare measured scores between groups, the Wilcoxon rank sum test was used. Data analysis relied on standard...
RESULTS

The study population consisted of 12 females and 2 males, 36 to 73 years of age (mean, 49 ± 11 years). Of these, 10 patients (2 females, 8 males; 36–73 years of age; mean, 48 ± 12 years) underwent immediate direct RLN anastomosis (group 1), whereas in 4 patients (4 females; 42–60 years of age; mean, 54 ± 7 years) no immediate repair was attempted (group 2).

In group 1, all patients were diagnosed with papillary thyroid cancer, occupying the right lobe of seven patients (70%) and the left lobe of three patients (30%). Eight patients (80%) underwent total thyroidectomy (stage I: 2, stage III: 3, and stage IVA: 3); subtotal thyroidectomy was done for the other two (20%; stage I and stage III). RLN injury was largely due to cancerous adhesions (7 patients, 70%), as opposed to iatrogenic transection (3 patients, 30%). Mean RLN defect was 3.4 mm (range, 2–5 mm). All patients submitted to injection laryngoplasty using Restylane (Medicis Aesthetic Inc, AZ) or Artesnese (Middleton Cosmetic Corp, Toronto, Ontario, Canada) filler (range, 0.3–0.8 cc; mean, 0.6 cc) for vocal cord medialization, although all displayed vocal cord atrophy beforehand. Mean timing of this procedure was 3.5 months (range, 2–6 months) postoperatively. Final follow-up exam was 19.3 months postoperatively (range, 14–23 months).

Four patients (group 2) did not undergo RLN anastomosis because the RLN defect was ≥5 mm (range, 5–7 mm; mean, 6 mm) or approximation was not achievable without undue tension. All patients submitted to injection laryngoplasty with filler (Restylane or Artesnese range, 0.3–0.8 cc; mean, 0.6 cc) for vocal cord medialization, although all displayed vocal cord atrophy beforehand. Mean timing of this procedure was 3.5 months (range, 2–6 months) postoperatively. All 14 patients were monitored in follow-up at 3, 6, and 12 months postoperatively.

Objective Outcome Analysis

In group 1, serial MPT determinations progressively increased. On the other hand, MPT values of group 2 changed little during follow-up. Compared with group 2, the MPT at 12 months was also significantly longer in group 1. (Fig 2).

Glottal gap scores of group 1 similarly declined; whereas those of group 2 did not. Furthermore, these scores differed significantly between at 12 months. (Fig 3).

Subjective Outcome Analysis

In group 1, GRBAS assessment (grade, roughness, breathlessness, asthenia, and strain) was significantly lower at 12 months postoperatively than at 3 months (Fig 4). The decrease in GRBAS indices of group 1 reflects an improvement in patient dysphonia over time.

Serial aspiration scores also progressively declined in group 1 (3 months: 1.3 ± 0.67; 6 months: 0.5 ± 0.53; 12 months: 0.3 ± 0.48), again with a statistically significant difference between 3- and 12-month values (1.3 ± 0.67 vs. 0.3 ± 0.48, P = 0.018). The aspiration scores of group 2 (3 months: 2 ± 0.82; 6 months: 1.75 ± 0.5; 12 months: 1.5 ± 0.58) at 3 and 12 months did not differ significantly (2 ± 0.82 vs. 1.5 ± 0.58, P = 0.63), and there was a statistically significant difference between groups 1 and 2 at 12 months (0.3 ± 0.48 vs. 1.5 ± 0.58, P = 0.01).

In group 1, VHI ratings by category (functional, physical, and emotional) were 27.7 ± 4.11, 28.9 ± 3.11, 26.6 ± 2.83, respectively at 3 months and 7.7 ± 1.16.

TABLE II.
Demographics for Group 2.

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender/Age</th>
<th>Diagnosis (stage)</th>
<th>Site (lobe)</th>
<th>Procedure</th>
<th>Cause of injury</th>
<th>Defect (mm)</th>
<th>Injection Laryngoplasty</th>
<th>Last Follow-Up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/56</td>
<td>papillary cancer</td>
<td>right</td>
<td>total thyroidectomy</td>
<td>iatrogenic transection</td>
<td>6</td>
<td>Restylane 0.3cc (POD 3 mo)</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>F/42</td>
<td>papillary cancer</td>
<td>right</td>
<td>total thyroidectomy</td>
<td>adhesion of tumor</td>
<td>7</td>
<td>Artesnese 0.8cc (POD 6 mo)</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>F/59</td>
<td>papillary cancer</td>
<td>right</td>
<td>total thyroidectomy</td>
<td>adhesion of tumor</td>
<td>6</td>
<td>Restylane 0.3cc (POD 2 mo)</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>F/60</td>
<td>papillary cancer</td>
<td>right</td>
<td>total thyroidectomy</td>
<td>adhesion of tumor</td>
<td>5</td>
<td>Artesnese 0.8cc (POD 3 mo)</td>
<td>14</td>
</tr>
</tbody>
</table>

TABLE III.
Glottal Gap Scale.

<table>
<thead>
<tr>
<th>No.</th>
<th>Gap Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No gap during phonation</td>
</tr>
<tr>
<td>1</td>
<td>Minimal gap</td>
</tr>
<tr>
<td>2</td>
<td>Small gap (up to ½ of posterior membranous vocal folds)</td>
</tr>
<tr>
<td>3</td>
<td>Moderate gap (up to 2/3 of posterior membranous vocal folds)</td>
</tr>
<tr>
<td>4</td>
<td>Complete glottal incompetence</td>
</tr>
</tbody>
</table>

software PASW Statistics 10.0 (SPSS, IBM, Inc, Chicago, IL). Values were expressed as mean ± standard deviation (SD), with statistical significance set at P < 0.05.
8.6 ± 2.37, 11 ± 1.05, respectively at 12 months following surgery. Ratings for each category declined significantly at 12 months, compared with 3 months (P = 0.002, P = 0.002, and P = 0.002, respectively).

VHI ratings of group 2 were 31.8 ± 2.75, 34.0 ± 2.16, and 31.3 ± 1.71, respectively at 3 months and 34.0 ± 2.16, 32.3 ± 0.96, and 33.3 ± 2.36, respectively at 12 months. Ratings at 3 months and at 12 months did not differ significantly in group 2 (P = 0.5, P = 0.25, and P = 0.125, respectively). At 12 months the total VHI rating for group 1 was significantly lower than that of group 2 (27.3 ± 3.13 vs. 99.5 ± 1.73, P = 0.001). Thus, patients of group 1 registered a perceived improvement in voice quality.

DISCUSSION

According to a prior study, overall rates of temporary and permanent RLN paralysis in the course of total thyroid lobectomy (unilateral or bilateral) are 5.1% and 0.9%, respectively, given routine nerve identification methods. A number of factors, including anatomic variation, extensive local and regional disease, previous surgery, and prior irradiation, may account for the risk of RLN paralysis during thyroid surgery. In this setting, RLN paralysis without recognized RLN injury is typically managed by delayed phonosurgical intervention (type I thyroplasty, arytenoid adduction, and vocal cord injection) and laryngeal reinnervation (direct RLN anastomosis, free-nerve grafting, ansa cervicalis/RLN anastomosis, and vagus/RLN anastomosis). Although voice quality is improved by these delayed phonosurgical intervention, these static procedures cannot prevent laryngeal muscle atrophy. However, laryngeal reinnervation can prevent the progressive loss of thyroarytenoid muscle tone and bulk that is seen with vocal fold denervation. For these reasons, immediate direct nerve anastomosis is standard practice in case of recognized RLN injury, if possible. Yumoto et al. have advocated immediate RLN reconstruction (immediate great auricular nerve interposition or direct RLN anastomosis) at the time of thyroid cancer resection as a means of ensuring excellent postoperative phonation, as opposed to waiving nerve reconstruction. Furthermore, Chou et al. reported renewed voice quality and other gains (MPT, GRBAS scores, and aspiration) in all instances where direct RLN anastomosis was done for RLN transection. Although vocal cord immobilization routinely resulted during a 6- to 24-month follow-up after RLN transection, only a single patient developed vocal cord atrophy when direct RLN anastomosis was performed. Without anastomosis, all patients regularly displayed vocal cord atrophy. In theory, muscle recovery...
should be closer to normal if a regenerating axon is promptly reconnected to its fibers. Kumai et al. showed that 10 weeks after RLN transection in rats, the total mass and individual fibers of thyroarytenoid muscle were reduced by nearly 50%. They also found that nerve terminals of the muscle disappeared completely 24 hours after denervation.23

Based on the above observations, we have performed immediate direct RLN anastomosis, with positive outcomes in terms of postoperative phonation and perceived voice quality. As objective findings, MPT was significantly longer in group 1. In group 1, the 12-month MPT surpassed the same-group 3-month value (Fig 2). Hence, we can assume that immediate direct RLN anastomosis may promote progressive laryngeal reinnervation, reflected as an incremental rise in MPT. Postoperative laryngoscopy further demonstrated that none of these group 1 patients had evidence of vocal cord atrophy, which may have helped diminish the glottal gap (whereas vocal cord atrophy did ensue in group 2). A diminished glottal gap decreases airflow leakage during phonation, increases MPT, and reduces breathiness (one GRBAS parameter). According to this study, the glottal gap of group 1 at 12 months declined significantly from that at 3 months. Results of Chou et al., with immediate direct RLN anastomosis, were similar (glottic gap: 6 months, 0.5 ± 0.53; 3 months, 2.3 ± 1.16).6 Moreover, when they compared GRBAS and aspiration

<table>
<thead>
<tr>
<th>Functional</th>
<th>Physical</th>
<th>Emotional</th>
</tr>
</thead>
<tbody>
<tr>
<td>My voice makes it difficult for people to hear me</td>
<td>I run out of air when I talk</td>
<td>I’m tense when talking with others because of my voice</td>
</tr>
<tr>
<td>People have difficulty understanding me in a noisy room</td>
<td>The sound of my voice varies throughout the day</td>
<td>People seem irritated with my voice</td>
</tr>
<tr>
<td>My family has difficulty hearing me when I call them throughout the house</td>
<td>People ask, “What’s wrong with your voice?”</td>
<td>I find other people don’t understand my voice problem</td>
</tr>
<tr>
<td>I use the phone less often than I would like</td>
<td>My voice sounds creaky and dry</td>
<td>My voice problem upsets me</td>
</tr>
<tr>
<td>I tend to avoid groups of people because of my voice</td>
<td>I feel as though I have to strain to produce voice</td>
<td>I am less out-going because of my voice problem</td>
</tr>
<tr>
<td>I speak with friends, neighbors, or relatives less often because of my voice</td>
<td>The clarity of my voice is unpredictable</td>
<td>My voice makes me feel handicapped</td>
</tr>
<tr>
<td>People ask me to repeat myself when speaking face-to-face</td>
<td>I try to change my voice to sound different</td>
<td>I feel annoyed when people ask me to repeat</td>
</tr>
<tr>
<td>My voice difficulties restrict my personal and social life</td>
<td>I use a great deal of effort to speak</td>
<td>I feel embarrassed when people ask me to repeat</td>
</tr>
<tr>
<td>I feel left out of conversations because of my voice</td>
<td>My voice is worse in the evening</td>
<td>My voice makes me feel incompetent</td>
</tr>
<tr>
<td>My voice problem causes me to lose income</td>
<td>My voice “gives out” on me in the middle of speaking</td>
<td>I’m ashamed of my voice problem</td>
</tr>
</tbody>
</table>

The voice handicap index (VHI), incorporating functional, physical, and emotional categories, was used by patients to perceptually rate the quality of their own voices.17 Each 10-question category (total of 30 questions) calls for scored responses of “never” (0), “almost never” (1), “sometimes” (2), “almost always” (3), or “always” (4). All 30 responses were summed, for a total VHI score of 0–120, with 0 as normal voice.

![Fig. 2. Maximum phonation time (MPT). In group 1, MPT increased significantly between 3 and 12 months (4.4 ± 0.84 sec vs. 11.7 ± 0.95 sec, P = 0.002). However, values in group 2 remained flat (3.25 ± 0.5 vs. 3.5 ± 1.0, P = 0.56). Compared with group 2, MPT value at 12 months was significantly longer in group 1 (11.7 ± 0.95 sec vs. 3.5 ± 1.0 sec, P = 0.001). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

![Fig. 3. Glottal gap. In group 1, glottal gap score declined significantly at 12 months postoperatively, compared with same-group value at 3 months (0.3 ± 0.48 vs. 2.2 ± 0.42, P = 0.002). At 12 months, glottal gap scores of groups 1 and 2 differed significantly (0.3 ± 0.58 vs. 3.5 ± 0.58, P = 0.001). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
scores of eight patients undergoing immediate direct RLN anastomosis with 4 patients who did not undergo nerve repair, a decline in GRBAS and aspiration scores of treated patients was observed at 6 months postoperatively (grade, 0.38 ± 0.52; roughness, 0.5 ± 0.53; breathiness, 0.5 ± 0.93; asthenia, 0.13 ± 0.35; strain, 0.13 ± 0.35; and aspiration, 0.25 ± 0.46), compared with scores at 3 months (grade, 1.75 ± 0.71; roughness, 1.5 ± 0.53; breathiness, 1.38 ± 0.74; asthenia, 1.25 ± 1.71; strain, 1.13 ± 0.83; and aspiration, 1.13 ± 0.64). Our findings were similar: GRBAS and aspiration scores of group 1 were lower at 12 months, compared with scores at 3 months.

Although all patients suffered vocal cord immobility after RLN injury, as determined by rigid laryngoscopy during follow-up (at 3, 6 and 12 months), medial positioning of the vocal cord was retained without atrophy in group 1. Both cords were thereby free to oscillate synchronously and symmetrically for reduced aperiodicity and perturbation, more “pure” tones, and significant improvements in postoperative perceptual evaluations (GRBAS and VHI).³

As for study limitations, defect size of RLN was different significantly between group 1 and 2. (3.4 ± 1.0 mm vs. 6 ± 0.7mm, P = 0.002), which can affect outcome; the more nerve defect there is, the more difficult it is for laryngeal reinnervation. At the different aspect, we could exclude the effect of spontaneous approximation of severed nerve ends in group 2. In addition to the aforementioned limitation in using MPT as a test for phonation, male/female disparities must be considered. Generally, MPTs of males are longer than those of females.¹⁶ The two males of group 1 were thus factored when comparing MPT results between groups. We also performed injection laryngoplasty on all patients to...
medialize vocal cords, which had the potential to cloud the pure effects of surgical anastomosis. However, the 12-month follow-up period was more than adequate for the temporary effects of injected filler to subside. We therefore felt safe in assuming that any improvement of phonation or perceived voice quality truly resulted from immediate direct anastomotic repair.

CONCLUSION

Patients submitting to immediate direct RLN anastomosis demonstrated improved phonation and perceptually rated voice quality compared with patients who did not undergo repair. Consequently, we can verify the therapeutic effect of nerve anastomosis for laryngeal reinnervation in this study.

BIBLIOGRAPHY