

Early Versus Late Injection Medialization for Unilateral Vocal Cord Paralysis

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Objectives: To evaluate whether the timing of early (≤ 6 months from time of nerve injury) vs. late (> 6 months) injection medialization laryngoplasty impacts the need for subsequent open-neck reconstruction to restore vocal function in patients with unilateral vocal cord paralysis.

Study Design: Retrospective chart review.

Methods: A total of 112 outpatient or hospitalized adults with dysphonia resulting from postsurgical or idiopathic unilateral vocal cord paralysis were identified who were injected as initial treatment within 1 year of onset of their paralysis. All subjects underwent awake, transoral, paraglottic injection with absorbable hyaluronic-acid gel. Patients with documented recovery of vocal cord mobility (22), active disease directly affecting the recurrent laryngeal nerve (8), < 3 months of follow-up after injection (time for gel to be reabsorbed) (34), or deaths within 1 year after the onset of paralysis (13) were excluded, leaving a study population of 35 patients.

Results: Twenty of 32 (62.5%) patients with early injection medialization maintained an adequate voice, obviating the need for open-neck phonosurgical reconstruction; their follow-up from onset of paralysis ranged from 4.0 to 41.8 months (mean 15.2). None of the three patients undergoing late injection (> 6 months postparalysis) avoided phonosurgical reconstruction ($P = .03$, χ^2 test).

Conclusions: Patients receiving early injection medialization for vocal cord paralysis were less likely to require transcervical reconstruction. We believe that early medialization creates a more favorable vocal cord position for phonation that can be main-

tained by synkinetic reinnervation, in contrast to the final position of a lateralized vocal cord being determined solely by reinnervation.

Key Words: Vocal cord paralysis, injections, dysphonia, larynx/surgery.

Level of Evidence: 3b.

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INTRODUCTION

Unilateral vocal cord paralysis (UVCP) leads to glottic insufficiency, which can result in dysphonia, weakened cough, aspiration, and pneumonia. A temporally limited surgical insult to the vagus nerve or recurrent laryngeal nerve (RLN) from neck or cardiothoracic surgery is the most common cause for this problem, with idiopathic processes or extra-laryngeal malignancies being frequent sources of vocal cord immobility in other patients.¹ In the acute setting, an injection medialization laryngoplasty can be helpful for temporarily restoring glottic competence, thereby improving voice and potentially reducing aspiration.^{2,3} Injection medialization procedures can be performed with topical anesthesia either at the hospital bedside or in the clinic, using either transoral⁴ or percutaneous⁵ methods.

We have observed that patients treated early on for UVCP with an injection medialization using a temporary material often do not need further permanent transcervical medialization procedures even when their immobility lasts beyond the expected spontaneous neural recovery period. Acoustically, their voice outcomes rival those achieved by other patients treated with open laryngeal framework surgery. Endoscopic examination shows that these patients have immobile but favorable vocal cord positioning for phonation, suggesting near optimal synkinetic reinnervation. Most important, this pattern seems more prevalent in those receiving their first injection laryngoplasty within 6 months of their UVCP onset. We believe that the residence time of the temporary implant material allows for a well-positioned vocal cord during the reinnervation period. The purpose of this study was to evaluate the need for permanent transcervical framework surgery in two UVCP patient cohorts based on when they were injected with an absorbable material. We sought to test the hypothesis

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that early injection may obviate the need for future voice restoration surgery.

MATERIALS AND METHODS

The Institutional Review Board (IRB) of Massachusetts General Hospital approved this study. A retrospective chart review was performed on all adult patients initially presenting at our institution and diagnosed during awake endoscopy with postsurgical or idiopathic UVCP. This review, conducted between July 2005 and July 2009, identified 112 patients with unilateral vocal cord paralysis who underwent injection medialization as initial treatment within 1 year of onset of their paralysis. The date of UVCP onset was defined as the operation date for postsurgical dysphonia patients or by the patient's report of dysphonia onset for those with idiopathic paralysis. Patients were included only if they received at least one awake, transoral, paraglottic injection laryngoplasty with an absorbable hyaluronic acid gel (Restylane, Q-Med AB, Uppsala, Sweden); no patients received vocal cord injections with other types of materials. No patients underwent a transcutaneous approach or general anesthesia for their injection medialization(s); however, one patient required intravenous sedation in the operating room. All patients had complete unilateral vocal cord immobility (UVCI) on the date of their first injection. A minority of patients underwent a second (or potentially a third) paraglottic injection if they presented with complaints of recurrent dysphonia during follow-up and were noted to have glottic insufficiency on examination at that time.

Following their initial diagnosis and first injection medialization, patients were excluded as follows: 13 died within 1 year of the onset of their UVCP; 22 recovered vocal cord mobility; 8 had persistent, active disease affecting the RLN; and 19 were lost to follow-up after their first injection, with most not residing regionally. In addition, at the time of data collection, 15 had <3 months of follow-up after their last injection. (In the authors' experience, 3 months represents an outside estimate for the time required for paraglottic hyaluronic acid gel to be reabsorbed to the point where patients with persistent UVCI once again become dysphonic.)

For the purposes of this study, an injection medialization laryngoplasty was classified as early if the subject received his or her first injection up to 6 months after the onset of UVCP. An injection was classified as late if it was received beyond 6 months (but <1 year) after UVCP onset. Any given patient's placement into one group or the other was based solely on the timing of his or her presentation. A patient was defined as having idiopathic UVCP if all of the following criteria were met: imaging (computed tomography [CT] or magnetic resonance imaging [MRI] scan) from the skull base to the aortic arch demonstrated no laryngeal pathology or abnormalities along the course of the vagus nerve or RLN; there was no history of prolonged intubation, laryngeal trauma, or neck radiation; there was no systemic (e.g., autoimmune disorder or stroke) illness known to cause vocal cord immobility; and awake endoscopy demonstrated no intrinsic laryngeal pathology in the region of the cricoarytenoid joints.

RESULTS

A study cohort of 35 patients (18 male, 17 female; average age 62 years [range 30–82] at the time of dysphonia onset) met the inclusion criteria for the study. Seven of the 35 had their first medialization injection performed at the bedside (with subsequent injections performed in the office, if required), 27 were injected solely in the office, and 1 was done in the operating room with awake

sedation. Details regarding demographics, cause of vocal cord immobility, length of follow-up, number and timing of vocal cord injections, classification into early or late injection groups, and ultimate need/timing of open neck medialization surgery are presented in Table I. None of the study participants were under the care of the authors prior to the onset of their dysphonia.

Multiple injections were required in some of the patients due to ongoing glottic insufficiency and recurrent dysphonia following clinical resorption of the paraglottic gel. In the authors' experience, the voice enhancement from these injections typically lasts approximately 3 months, although it sometimes fades sooner due to redistribution of the hyaluronic acid gel within the paraglottic region. Thirteen of the 32 patients in the early injection group had a second injection, an average of 4.2 months after their dysphonia onset, and 4 of those 13 patients required a third injection, an average of 5.6 months after their dysphonia onset.

Eighty-six percent (30/35) of patients had postsurgical dysphonia from a procedure where either the RLN or vagus nerve was at risk. The recurrent laryngeal nerve was known to be transected in 3 patients, and it was repaired primarily in all of them. These 3 patients each underwent injection medialization at or before 6 months from the time of their injury (early group), and none required transcervical surgery (follow-up in this sub-group ranged from 8.5 months to 1 year after their injury).

Of the 5 patients where the RLN or vagus nerves were not at risk for surgical injury, 1 patient had immediate postoperative dysphonia following a short abdominal surgery during which she underwent endotracheal intubation. The remaining 4 patients were classified as idiopathic based on their history (usually in the context of a respiratory tract infection) and the appropriate negative workup as detailed in Materials and Methods.

Fifteen of 35 patients ultimately required transcervical laryngeal framework surgery. The decision for surgery was not based on a specific objective or subjective finding but rather a persistently immobile vocal cord, with glottic insufficiency and accompanying dysphonia. Surgical procedures included at least a medialization laryngoplasty with Goretex.^{6,7} Four of these 15 patients in the early injection group and 1 in the late injection group also underwent a simultaneous adduction arytenopexy and cricothyroid subluxation.^{6,8,9} The number of patients who required transcervical medialization surgery after an early injection (≤ 6 months) was significantly less ($P=0.03$, χ^2 analysis) compared with those receiving a late injection (>6 months)(Fig. 1). One patient with idiopathic vocal cord paralysis reported her dysphonia onset as occurring approximately 6 months prior to her presentation. If she is included in the late injection group, rather than the early group, then, by χ^2 analysis, the difference between the two groups does not reach statistical significance ($P=0.1$).

DISCUSSION

The information herein revealed that patients were less likely to require a permanent implant medialization and/or arytenoid repositioning procedure if they received

TABLE I.
Unilateral Vocal Cord Paralysis Patient Cohort Characteristics.

Age at Injury	Gender	Cause of Immobility	Follow-up Since Injury (Months)	Months from Injury to First Injection	Months from Injury to Second Injection	Months from Injury to Third Injection	Transcervical Medialization Surgery	Months from Injury to Open Surgery
Early injection group (n = 32)								
54	M	Lung resection for lung cancer	41.8	0.1			Y	39.7
42	F	Thyroidectomy (RLN cut and repaired)	12.2	0.1			N	
75	F	Tracheal resection	5.2	0.1			Y	5.2
48	F	Thyroidectomy	12.7	0.1			N	
76	F	Thoracic aortic aneurysm repair	8.0	0.2			Y	5.6
63	M	Hematoma after thyroid FNA	4.0	0.2			N	
59	M	Lung resection for infection	41.1	0.3			Y	2.8
66	M	Thoracic aortic aneurysm repair	17.7	0.3			Y	15.1
52	F	Thyroidectomy	11.1	0.6			N	
75	M	Thyroidectomy	12.9	1.2			N	
63	M	Carotid endarterectomy	5.4	1.6			N	
68	F	Esophagectomy	7.4	1.8			N	
79	M	Idiopathic	7.3	2.1			Y	3.9
31	M	Thyroidectomy	27.7	2.7			N	
67	M	Idiopathic	24.7	3.0			N	
64	F	Thyroidectomy	18.4	4.0			Y	18.4
81	F	Thyroidectomy (RLN cut and repaired)	8.5	4.0			N	
77	F	Aortic arch replacement	8.6	4.6			N	
38	F	Parathyroidectomy	8.0	4.9			Y	8.0
78	M	Lung resection for lung cancer	13.1	0.1	2.5		N	
80	F	Thyroidectomy	11.4	0.7	3.9		N	
61	F	Carotid body tumor resection	7.1	0.8	2.5		Y	6.2
68	F	Idiopathic (brief intubation)	6.7	1.6	3.2		N	
73	M	Thoracic aortic aneurysm repair	24.1	1.7	3.5		Y	12.6
66	F	Lung biopsy	33.7	2.0	4.1		N	
50	M	Parathyroidectomy (RLN cut and repaired)	11.3	2.2	4.3		N	
44	F	Thyroidectomy	20.3	4.1	7.2		Y	10.0
55	F	Idiopathic	10.6	6.0	10.6		N	
68	M	Thoracic aortic aneurysm repair	12.4	0.3	2.2	5.1	N	
53	M	Lung resection for lung cancer	12.2	0.4	3.2	6.0	Y	12.2
83	M	Idiopathic	16.2	2.5	3.5	5.9	N	
30	M	Medastinoscopy	23.1	2.5	3.2	5.3	N	
Average			15.2	1.8	4.2	5.6		
Median			12.2	1.6	3.5	5.6		
Minimum			4.0	0.1	2.2	5.1		
Maximum			41.8	6.0	10.6	6.0		
Late injection group (n = 3)								
72	M	Carotid endarterectomy	8.4	6.1			Y	8.2
70	M	Thyroidectomy	43.4	9.2	11.2		Y	43.4
49	F	Thyroidectomy	15.0	6.5	7.5		Y	14.2
Average			22.3	7.3	9.3			
Median			15.0	6.5	9.3			
Minimum			4.0	0.1	2.2			
Maximum			43.4	9.2	11.2			

RLN =recurrent laryngeal nerve.

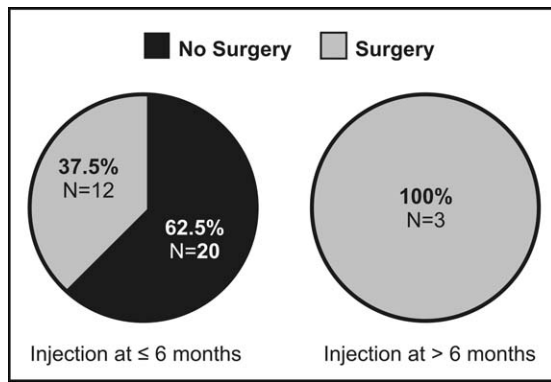


Fig. 1. Comparison of need for transcervical medialization laryngoplasty surgery in patients with unilateral vocal cord immobility who received their initial paraglottic vocal cord injection at early (≤ 6 months) versus late (> 6 months) time points.

an early injection medialization laryngoplasty with a reabsorbable implant material. These preliminary data suggest that medializing a paralyzed, abducted vocal cord with a temporary material can permanently influence the final vocal cord position. We believe this occurs because the vocal cord is moved to a favorable medial phonatory position during the time window of synkinetic reinnervation. Furthermore, it is more likely for synkinetic reinnervation to permanently maintain a medialized vocal cord in position than to adduct a lateralized vocal cord.

Defining the time window for the beginning and end point for synkinetic reinnervation is admittedly difficult, especially due to the disparity in causes of denervation, spectrum of anatomic injury, and variations in reinnervation patterns. Crumley described a chronic phase of RLN regeneration following a complete transection injury, during which regeneration has begun and clinical evidence of improvement may be seen, as occurring 4 to 5 months post-injury.¹⁰ In addition, in centers that have performed large numbers of ansa cervicalis-to-RLN anastomoses for treatment of UVCP, the average time for onset of vocal improvement following a surgery, which, by definition, requires transection of the RLN, is 4 months, suggesting that reinnervation has started by that time as well.¹¹

For those with less severe neural injuries (but persistent vocal fold immobility), it is likely that the vocal cord should be optimally positioned even earlier than 4 months, since the reinnervation window may begin sooner in these patients. Because the severity of the neural injury is usually unknown (unless the RLN or vagus nerve has been transected), it is our group's strategy to intervene with an injection laryngoplasty as soon as possible, often at the patient's bedside or within the first few weeks following their dysphonia onset. Given the temporary duration of the injected hyaluronic acid gel, patients will sometimes require a second injection and rarely a third to ensure that the vocal cord is adequately positioned during the reinnervation window. Our impression is that in the large majority of patients, the clinical benefit of the reinnervation window likely begins within 6 months from the onset of injury, which has been similarly observed by others (personal commu-

nication: Roger Crumley). This was the basis for the 6-month cutoff between early and late injection groups.

Some patients in the early injection group elected for medialization surgery after an initial injection failed to provide lasting vocal benefit. Specifically, 4 of the 11 patients in the early injection group who went on to have surgery were injected within 2 months from their dysphonia onset, but when their voices worsened after the injection faded, they chose to have open laryngoplasties, all of which were performed before 6 months had elapsed since the onset of their UVCP. It is unknown whether, after a second injection, they would have achieved a lasting favorable vocal cord position, obviating the need for surgery.

In addition to the notion that temporary medialization of a vocal cord allows for a better final resting position once synkinetic reinnervation is complete, a paralyzed but medialized vocal cord may also experience sensory (vibro-tactile) stimulation from physical contact with the contralateral (mobile) vocal cord that would not otherwise be present in the absence of an injection. Tactile stimulation of denervated muscles has been shown to improve functional recovery after lesion of the rat facial^{8,9} and hypoglossal nerves¹⁰ and is associated with reduced polyinnervation of the reinnervated muscles without reduction of misrouting by regenerating axons. In a variation on this theme, as far back as the mid-1800s, mirror-guided application of electric current (faradism and galvanism)¹⁴ was applied to stimulate recovery of UVCP and prevent laryngeal muscle atrophy, and these ideas are behind some of the current concepts of electrical laryngeal pacing.¹¹

A recognized weakness of the present study design is that subjects were not randomized into the early (≤ 6 months) versus late (> 6 months) injection groups. This creates a potential selection bias because the likelihood of spontaneously recovering an adequate voice in the absence of unilateral vocal cord mobility (with or without injection) may be expected to decrease across the first year after UVCP onset. Sulica, in his meta-analysis of the natural history of idiopathic vocal cord paralysis, brings up this same concept.¹² In that article, across all 717 cases from 20 papers from 1941 to 2005, "complete recovery of voice" was reported in an average of $52 \pm 17\%$ of patients and "complete recovery of motion" was reported in an average of $36 \pm 22\%$. It is not mentioned (or perhaps knowable) what percent of these patients underwent any sort of temporary paraglottic augmentation, which may, as this article suggests, actually influence final voice outcome. In addition, this present study cohort specifically excludes all patients with any return of function, whereas there is no trivial way to parse what subset of patients in the above referenced article had vocal recovery but not return of vocal cord motion. While it could be argued that the results of this study (62.5% of all patients with persistent paralysis that were injected early did not have dysphonia requiring further corrective surgery) are within these reported ranges and that a temporary injection does not influence final vocal cord position, it is difficult to draw any conclusions when comparing these disparate groups.

Thus, in the present study, the statistically significant association between receiving an early medialization injection and the reduced need for open framework surgery is not necessarily causative. A prospective study is needed where all participants are enrolled within a maximum number of months after UVCP onset (e.g., 3) and are then randomly assigned an immediate or delayed initial injection time point. However, if postponement of medialization injection does indeed increase the need for open-neck phonosurgery, then such a delay for the purpose of experimentation must be ethically scrutinized. Alternatively, exploration of this phenomenon may be required in an animal model.

Incomplete follow-up is another potential weakness with almost any retrospective data, and this study is no exception. From the original potential cohort of 112 patients, 19 patients never returned after their initial injection, and an additional 15 patients did not have follow-up beyond 3 months from their last injection at the time of data collection. Of these 34 patients, only 1 would have been classified into the late injection group. While excluding all of these patients who were lost to follow-up introduces additional bias, it is speculated that at least some either recovered vocal cord mobility or had an immobile but favorably positioned vocal cord, resulting in a good, or at least serviceable, voice. In fact, at least 2 of these patients had subsequent documentation in their medical records by other physicians indicating a good voice; because these patients were not able to be reexamined (and the reason for their return of voice cannot be known for certain), they have not been included in the study cohort. Those with persistent dysphonia, on the other hand, were more likely to return for continued management (e.g., another injection or transcervical medialization surgery).

CONCLUSIONS

This preliminary, retrospective study suggests an association between early vocal cord medialization injection and a reduced need for open-neck laryngeal framework surgery in patients with persistent UVCP. In hospitalized patients in whom the injury is suspected and diagnosed, timely bedside medialization injection may therefore have benefit beyond the immediate reduction in aspiration risk and improved ability to cough and communicate. A similar advantage of avoiding additional cervical surgery may exist for UVCP patients who are

injected for the first time in the office as well. Colleagues who perform surgeries where the RLN or vagal nerve is at risk for injury may now have even more reason to seek early consultation from a laryngologist prepared to offer a temporizing vocal cord injection with benefits that potentially outlast the longevity of the injected substance. Also, the use of a dissolvable injectate avoids the added complexity of needing to remove it in the event that the UVCP is permanent and the patient ends up requiring transcervical medialization surgery. Subsequent prospective and potentially randomized studies may help further define the causal relationship between the timing of injection procedures and subsequent need for open framework surgery.

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