Systematic Review of Laryngeal Reinnervation Techniques

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ABSTRACT

Objectives: To systematically review outcomes of reinnervation techniques for the management of unilateral vocal fold paralysis (UVFP).
Methods: A search was conducted of PubMed, Embase, and Cochrane databases for English-language studies published between 1966 and 2009 on the surgical management of UVFP. Studies were excluded if they reported on bilateral vocal fold paralysis, used non-human subjects, or did not assess clinical outcomes. Outcomes of interest were visual analysis, acoustic analysis, perceptual analysis, and electromyography (EMG).
Results: Of 686 initial studies, 14 studies encompassing 329 patients were eligible for analysis. All studies had a case-series design. Of reported patients, 60.2% were male, with mean (range) age 51 (12-79). The most common reinnervation technique was ansa cervicalis-to-recurrent laryngeal nerve (RLN), which was most commonly performed following thyroidectomy (43.5%). Other techniques with reportable outcomes included primary RLN anastomosis, ansa-to-RLN combined with cricothyroid muscle-nerve-muscle pedicle, ansa-to-thyroarytenoid neural implantation, ansa-to-thyroarytenoid neuromuscular pedicle, and hypoglossal-to-RLN. Median postsurgical follow up was 12 months, and mean (SD) time to first signs of reinnervation was 4.5 (2.9) months. Visual analysis of glottic gap showed the greatest mean (SD) improvement with ansa-to-RLN, from 2.25 (0.886) to 0.75 (0.886) mm (p<0.01). Acoustic analysis showed greatest improvement with neural implantation, with a change in mean (SD) phonation time from 7 (1.22) to 16 (5.52) seconds (p <0.01). Perceptual analysis and EMG demonstrated improvement in all studies.
Conclusions: Reinnervation is effective in the management of UVFP, although the specific method may be dictated by anatomical limitations. Prospective studies utilizing uniform and consistent outcome parameters are necessary.

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INTRODUCTION

- Unilateral vocal fold paralysis (UVFP) is a common problem presenting to the otolaryngologist.
- Most frequent cause is recurrent laryngeal nerve (RLN) injury by extra-laryngeal malignancy, iatrogenic or idiopathic etiologies.
- RLN palsy is the most common serious complication of thyroid surgery, ranking among the leading reasons for litigation of surgeons
- Even with the use of physiologic nerve monitoring, temporary and permanent RLN palsy still occur at rates of 6% and 1%, respectively.
- In the United States between 1997 and 2009, the incidence of thyroid cancer increased by 6.4% per year.
- Regardless of the cause of nerve injury, optimal management of UVFP in the face of these rising trends in surgical thyroid disease is becoming an increasingly relevant issue.
- Exam findings include: forward-tilted arytenoid, loss of movement, loss of muscle tone, bowing, dysphonia, aspiration, synkinesis
- Surgical Interventions include: injection laryngoplasty, medialization thyroplasty, arytenoid adduction, reinnervation
- Laryngeal reinnervationtechniques:
  - Primary RLN anastomosis
  - Ansacervicalis-to-RLN neurorrhaphy (ansa-RLN)
  - Ansacervicalis-to-thyroarytenoid neural implantation (implantation)
  - Ansacervicalis-to-thyroarytenoid neuromuscular pedicle (NMP)
  - Hypoglossal-to-RLN neurorrhaphy (hypoglossal-RLN)
  - Cricothyroidmuscle-nerve-muscle neurotization (CT MNM).
- Supplementation with temporary injection (cymetra or gelfoam) until reinnervation is clinically evident.
- In light of the increasing rates of certain surgical procedures, the greatest utility in reinnervation lies in the ability to immediately repair an injured nerve if identified intraoperatively
- Successful animal studies do not always predict the results of analogous procedures in human patients.
- Clinical reinnervation studies in human subjects have been done along with prior narrative review articles.
- Consistent recommendations are lacking and reports on the different techniques vary.

METHODS AND MATERIALS

- Literature Search of medline and Cochrane databases by Medical Subject Heading (MeSH) terms filtered for English language and human studies:
  - "recurrent laryngeal nerve" (subheading "surgery") and "unilateral vocal fold paralysis" (subheading "surgery").
  - Corresponding word combinations: "Recurrent Laryngeal Nerve/surgery"[MAJR] AND ("humans"[MeSH Terms] AND English[lang]) OR "Vocal Cord Paralysis/surgery"[MeSH Terms] AND ("humans"[MeSH Terms] AND English[lang]).
- Reference lists of identified articles were screened for additional relevant studies.
- Selection of Studies
  - Two independent reviewers (B.A. and E.M.) assessed for the following exclusion criteria: Medialization not involving reinnervation, posterior cricoartytenoid reinnervation for bilateral vocal fold paralysis, review articles, duplicate subjects, absence of preoperative values, novel technique
- Quality checks based on four questions for case series:
  - Purposes of data collection
  - Consecutive samples
  - Follow up period at least one year
  - Explanation for lack of postoperative data/follow up
- Extraction and Analysis of Data: Design, intervention, outcome measure and parameters, duration of paralysis/follow up/time until first signs of reinnervation, age, sex, and etiology of UVFP
- Data was recorded including mean values, standard deviations, confidence intervals, and/or p-values when available.
- Generalized scales constructed when possible
- No further statistical analysis due to ambiguities in methodology and follow up data in several studies

RESULTS

Medline relevant studies n = 686 → 20 citations → 10 citations → 14 citations → Data Extraction

- Title/abstract screened for relevance
  - Irrelevant technique
  - Non-human studies
  - Bilateral paralysis
  - Review article
- Full text screened for relevance:
  - Duplicate patients (n=7)
  - Lacking preoperative values (n=1)
  - Novel approach (n=2)
- Additional papers found by reference search n=4

Surgical Subjects

Male	Female	Mean Age	Age Range	Presurgical observation (months)	Follow up Range (median) in months	First Signs of Reinnervation (months)
29%	71%	51	12-79	Range 4-108 months	Range 0-120 months	Range 2-12 months
					Overall Median: 12 months	Overall Median: 4 months

Etiologies

Technique	Etiology	% of Surgical Subjects
Primary RLN	Thyroid surgery or cancer	80%
	Parathyroid surgery	20%
Ansa-RLN	Thyroid surgery or cancer	78%
	Idiopathic	13%
Ansa-RLN +/- CT MNM	Idiopathic	21%
	Thyroid surgery or cancer	16%
NMP	Thyroid surgery or cancer	23%
	Idiopathic	16%
Implantation	Thyroid surgery or cancer	40%
	Spinal surgery	30%
Hypoglossal	Mediastinal mass surgery	34%
	Idiopathic	22%

Vertical Height Difference[1]

Study	Intervention	Subjects	Preop	Postop	p value
Lorenz*†	Ansa/Ansa+ MNM	21	0.14	0.2	0.17
Lee*	Ansa/Ansa+ MNM	13	0	0	N/A

Glottic Chink[2]

Study	Intervention	Subjects	Preop (SD)	Postop (SD)	Confidence Interval
Chou	Primary RLN	8	2.25(1.16)	0.5 (0.53)	N/A
Zheng	Ansa	8	2.26	0.75	N/A
Lorenz*‡†	Ansa/Ansa+ MNM	21	0.68	0.19	(0.04-0.9)
Lee*	Ansa/Ansa+ MNM	13	1	0.1	N/A
Maronian*	Ansa/NMP	7	1.85	0.28	N/A
Su***	Implantation	9	2	0	N/A

TVF Edge[3]

Study	Intervention	Subjects	Preop	Postop	Confidence Interval	p value
Lorenz*†‡	Ansa/Ansa+ MNM	21	0.69	0.25	(0.07-0.84)	0.026
Lee*	Ansa/Ansa+ MNM	13	1	0.66	N/A	N/A

Supraglottic Effort[4]

Study	Intervention	Subjects	Preop	Postop	Confidence Interval	p value
Lorenz*†	Ansa/Ansa+ MNM	21	0.78	1.34	(0.37-4.83)	0.66
Lee*	Ansa/Ansa+ MNM	13	1.3	0.95	N/A	N/A

Mucosal Wave[5]

Study	Intervention	Subjects	Preop	Postop	Confidence Interval
Crumley**	Ansa	5	1	0.2	(0.24-1.36)

Arytenoid Position[6]

Study	Intervention	Subjects	Preop	Postop	Confidence Interval	p value
Lorenz*†	Ansa/Ansa+ MNM	21	0.53	0.86	(0.12-2.46)	0.42
Lee*	Ansa/Ansa+ MNM	13	1	1.1	N/A	N/A
Su***	Implantation	9	1.67	3	N/A	N/A
Maronian*	Ansa/NMP	7	1	0	N/A	N/A

Arytenoid Movement[7]

Study	Intervention	Subjects	Preop	Postop
Zheng	Ansa	8	0	0
Maronian*	Ansa/NMP	7	0.14	0.43
Su***	Implantation	9	0	0

TVF Position[8]

Study	Intervention	Subjects	Preop	Postop	Confidence Interval	p value
Maronian*	Ansa/NMP	7	2.38	2.38	N/A	N/A
Lorenz*†	Ansa/Ansa+ MNM	21	0.38	0.33	(0.09-1.2)	0.092
Lee*	Ansa/Ansa+ MNM	13	1.23	1.13	N/A	N/A
Su***	Implantation	9	2.25	2.81	N/A	N/A

[1]Scale: Absent vs Present
[2]Scale 0 – 3: Complete closure -> Fully incomplete
[3]Scale 0 – 3: Normal -> Severely Bowed
[4]Scale 0 – 3: Normal -> Severe Effort
[5]Scale: Normal vs Abnormal
[6]Scale 0 – 3: Symmetric-> Severely tilted forward
[7]Scale 0 – 2: Asymmetric -> Normal
[8]Scale 0 – 3: Normal -> Lateral
*Injection laryngoplastysupplementation gelfoam or cymetra
**Preoperativeteflon injection laryngoplasty
***Medializationthyroplasty supplementation
†Preoperative value given as baseline probability of abnormality and postoperative value given as odds ratio of abnormality. Scale not utilized
‡Statistical significance noted

GRBAS Perceptual Analysis[1]

Study	Intervention	Subjects	Grade Preop (SD)	Grade Postop (SD)	Roughness Preop (SD)	Roughness Postop (SD)	Breathiness Preop (SD)	Breathiness Postop (SD)	Asthenia Preop (SD)	Asthenia Postop (SD)	Strain Preop (SD)	Strain Postop (SD)
Chou†	Primary RLN	8	1.75(0.71)	0.375(0.52)	1.5(0.53)	0.5(0.53)	1.375(0.74)	0.5(0.93)	1.25(0.71)	0.125(0.35)	1(0.76)	0.25(0.46)
Olson*	Ansa	11	1.75	1.02	3	0.78	1.21	0.56	1.03	0.64	0.98	0.91
Maronian*	Ansa	5	2	1.4	1.94	1.14	1.66	0.66	1.48	0.54	0.06	0
Maronian	NMP	3	1.8	0.53	1.6	0.67	0.9	0.2	0.76	0.3	0.43	0

CAPE-V Perceptual Analysis[2]

Study	Intervention	Subjects	Severity Preop (SD)	Severity Postop (SD)	Roughness Preop (SD)	Roughness Postop (SD)	Breathiness Preop (SD)	Breathiness Postop (SD)	Strain Preop (SD)	Strain Postop (SD)
Lee*	Ansa/Ansa+ MNM	13	100	35	100	30	100	0	100	66
Lorenz*†	Ansa/Ansa+ MNM	21	61.3(5.6)	37.9(7.3)	41.4 (5.3)	23.1(7.1)	53.3(6)	43.8(8)	24.7(5.6)	15.6(7.4)

Patient Perceptions[3]

Study	Intervention	Subjects	Preop	Postop
Chou†	Primary RLN	8	2	3
Smith‡	Ansa	5	0.9	2.55
Maronian*	Ansa	5	0	1.4
Lee*	Ansa/Ansa+ MNM	14	0.6	2.4
Maronian	NMP	3	0	1.67

Professional Perceptions[4]

Study	Intervention	Subjects	Preop	Postop
Smith‡	Ansa	5	1.49	2.39
Zheng	Ansa	8	0	2.5
Tucker	NMP	73	0	1.9
May*	NMP	29	0	1.86

Patient Perceptual Aspiration Rating[5]

Study	Intervention	Subjects	Preop (SD)	Postop (SD)
Chou†	Primary RLN	8	1.125(0.64)	0.25(0.46)

[1]Scale 0-3: Normal -> Severe dysphonia
[2]Scale 0-100: Normal -> Severe dysphonia
[3]Scale 0 – 3: No improvement -> normal voice
[4]Scale 0 – 3: Dysphonic -> normal voice
[5]Scale 0 – 3: Normal swallowing -> Severe aspiration
*Injection laryngoplastysupplementation with gelfoam or cymetra
†Statistical significance noted in all parameters
‡Arytenoidmedialization supplementation

Electromyography

Study	Intervention	Subjects	Thyroarytenoid Preop	Thyroarytenoid Postop	Cricothyroid Preop	Cricothyroid Postop	Head lift >Phonation
Maronian*	Ansa	2	All intactive	All active	N/A	N/A	Yest
Zheng	Ansa	3	All intactive	All active	N/A	N/A	N/A
El-Kashlan‡	Ansa + MNM	3	All intactive	All active	All intactive	All active	N/A
Maronian	NMP	2	All intactive	All active	Active	All active	Yest
Su†	Implantation	4	All intactive	All active	N/A	N/A	Yest
Paniello	Hypoglossal	5	All intactive	All active	N/A	N/A	N/A

Inactive: fibbrilations and involuntary motor unit action potentials (MUAP)
Active: presence of at least 20% voluntary motor unit action potentials and recruitment
*Injection laryngoplastysupplementation with gelfoam
†Medializationthyroplasty supplementation
‡Medialization and/or injection laryngoplasty

Shimmer and Jitter

Study	Intervention	Subjects	Jitter % Preop(SD)	Jitter % Postop (SD)	Shimmer % Preop(SD)	Shimmer % (SD) Postop
Zheng‡	Ansa	8	2.03(1.25)	0.43(0.23)	8.83(2.24)	3.22(2.11)
El-Kashlan**	Ansa + MNM	3	10.6	0.64	1.02	0.15
Su†‡	Implantation	9	2.19 (0.71)	0.54(0.31)	7.18(0.97)	2.47(1.22)
Paniello	Hypoglossal	5	7.75	0.87	10.5	3.5

Mean Phonation Time

Study	Intervention	Subjects	MPT (SD) Preop	MPT (SD)Postop
Chou‡	Primary RLN	8	4.9(1.3)	10(1.8)
Miyauchi§	Primary RLN	7	3.95(2.21) (PEI)	7.26(2.68) (PEI)
Smith*	Ansa	6	6.5	13.2
Miyauchi§	Ansa	63	3.95(2.21) (PEI)	7.05(2.93) (PEI)
Su†‡	Implantation	9	7(1.22)	16(5.52)
Paniello	Hypoglossal	5	2	15.6

*Arytenoid medialization supplementation
**Injection laryngoplasty with gelfoam and/or arytenoid medialization supplementation
†Medialization thyroplasty supplementation
‡Statistical significance noted for both parameters
§ Phonation efficiency index (PEI) = MPT/vital capacity

DISCUSSION

- All of the studied reinnervation techniques provide improvement in symptoms to varying degrees for perceptual, visual, EMG, and acoustics
- Association between etiology and the selection of certain procedures based on anatomic limitations and donor/proximal stump availability.
- Methodological quality, design, and reporting of most of the included studies was limited. Only four studies reported on statistical significance.
- Limitation: heterogeneity between different studies. Notably:
  - Deficiencies in supraglottic effort and arytenoid position seen for ansa-RLN These parameters were not measured in primary RLN, precluding direct comparison.
  - Supplemental laryngoplasty use
- Limitation: pooling of multiple techniques/outcomes within a single study.
  - Miyauchi et al: ansa-RLN and primary RLN.
  - Maronain et al: NMP and ansa-RLN.
  - Lee et al and Lorenz et al: ansa-RLN vs ansa-RLN combined with CT MNM.
- Aspiration was reported on in only one study (Chou et al)
- With exception of Miyauchi et al, most repairs took place several months to years after the initial surgical procedure. As stated earlier, one of the major advantages of reinnervation is the ability to immediately address nerve injury intraoperatively, potentially circumventing future surgical procedures.

CONCLUSIONS

- Each technique shows an overall degree of effectiveness
- Association between certain etiologies or anatomical limitations and the choice of reinnervation technique is noted.
- Quality of the current literature is low.
- Further studies using uniform and consistent outcome parameters are needed in order to make further direct comparisons between techniques.
- Prospective studies, preferably in the setting of immediate intraoperative repair, should be initiated using uniform and consistent outcome parameters.

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