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M E D I C I N E

# Injection laryngoplasty for unilateral vocal cord paralysis: does it make for a faster nerve recovery?

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# Injection Laryngoplasty: an Introduction

- Brunings 1911 introduced injection laryngoplasty (paraffin via indirect laryngoscopy)
- Teflon—shift in injection laryngoplasty in 1970s secondary to granuloma formation
- 1915: Erwin Payer developed method of operating on thyroid cartilage
- 1974: Isshiki and thyroplasty
- 1984: Dr Ford injection of collagen
- 1991: Dr Mikaelian fat injection laryngoplasty

# Types of injection material

## Chapter 31

### Vocal Fold Augmentation via Direct Microlaryngoscopy

# 31

#### 31.1 Fundamental and Related Chapters

Please see Chaps. 5, 8, 10, 14, 32, 33, and 34 for further information.

#### 31.2 Disease Characteristics

Vocal fold injection can be an extremely useful treatment method for a variety of voice disorders. There are different locations, injection materials and methods to perform vocal fold injection (see Chap. 14, "Principles of Vocal Fold Augmentation"). The advantage of injection augmentation versus open laryngeal procedures (laryngeal framework surgery) is the endoscopic and minimally invasive nature. Other advantages include a more direct visualization of the vocal fold pathology requiring treatment.

Injection augmentation can be divided into two specific anatomic locations, with subsequent different indications, materials, and methodologies applied to all of these locations. A superficial or medial vocal fold injection is performed for the treatment of vocal fold scarring or focal loss of lamina propria.

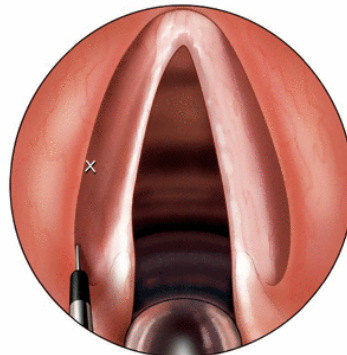


Fig. 31.1 Deep vocal fold augmentation locations

This technique is discussed in Chap. 32, "Superficial Vocal Fold Augmentation via Microlaryngoscopy."

Injection augmentation can also be carried out in a deep or lateral vocal fold position. This injection location is used to augment globally the vocal fold for cases of significant glottal incompetence due to:

- Vocal fold paralysis
- Vocal fold paresis
- Vocal fold atrophy
- Sulcus vocalis
- Severe vocal fold scar
- Soft tissue loss of the vocal fold(s)

#### 31.2.1 Material Selection

The *ideal* vocal fold injection material would be readily available, inexpensive, easy to use and completely biocompatible. The search for such a material has been ongoing for close to a 100 years, and significant advances in vocal fold injection material availability and design have occurred in the last 10 years. The original injection material was paraffin, which resulted in a significant foreign body response and rejection. Similar responses have occurred with Silicone injections as well as more recently with Teflon® vocal fold injections. An additional requirement of all future vocal fold injection materials will be a matching of the biomechanical properties of the material with the biomechanical properties of either the superficial aspect of the vocal fold (superficial layer of the lamina propria) or the deep aspect of the vocal fold (vocalis, thyro-arytenoid and lateral cricoarytenoid muscle).

The materials presently available for vocal fold injection include (see Chap. 14, "Principles of Vocal Fold Augmentation"):

- Autologous fat
- Radiess® (calcium hydroxylapatite)
- Teflon®
- Gelfoam®
- Radiess Voice Gel®
- Bovine collagen-based products (Zyplast®, Zyderm®)
- Human collagen-based products (Cymetra®, Cosmoplast®, Cosmoderm)
- Hyaluronic acid-based products (Hyalafarm®, Hyalafarm Plus®, Restylane®, Perlane®)
- Autologous fascia (minced)

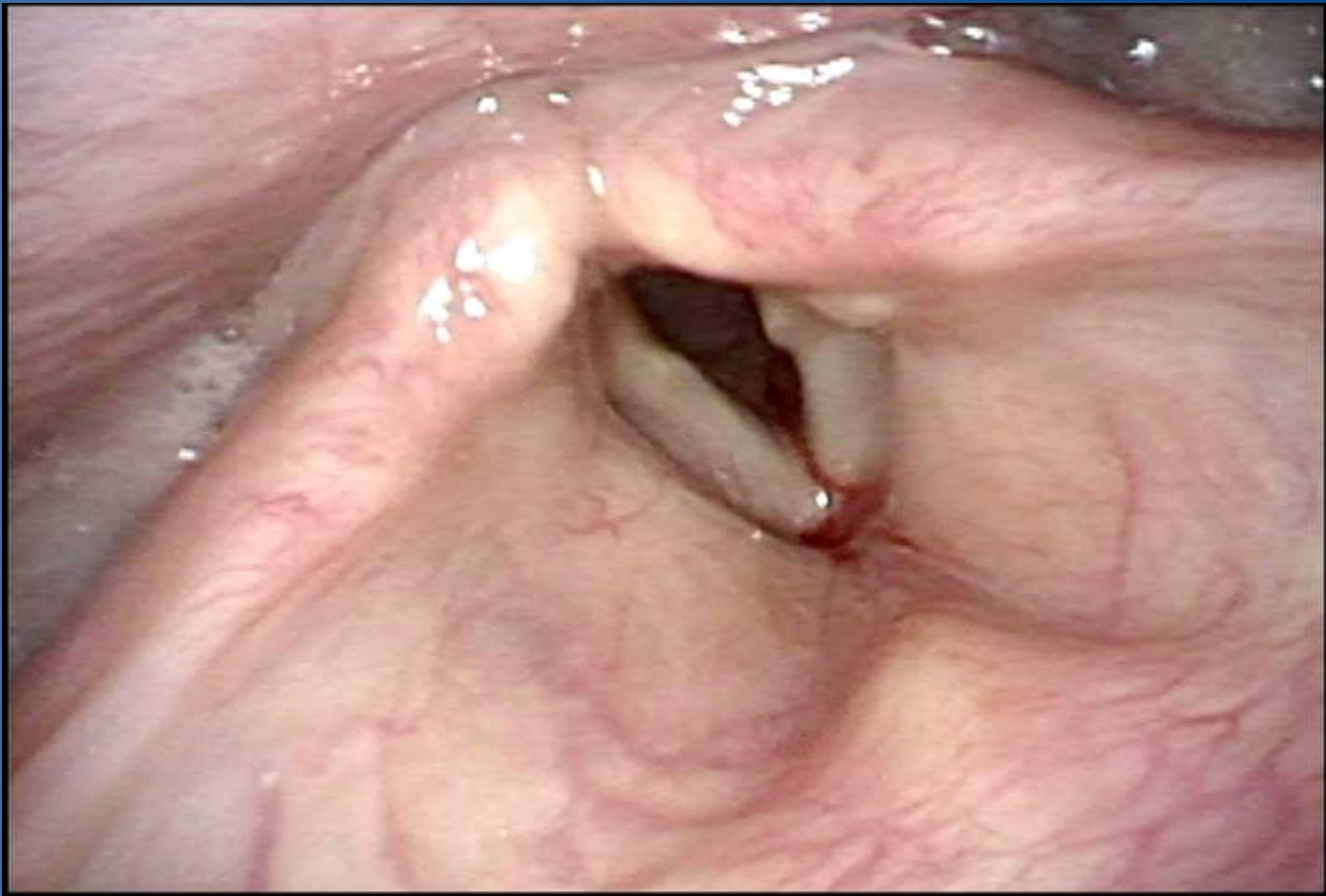
# Types of injectate

Short Term	Longer Lasting
Bovine gelatin-Gelfoam TM	CAHA
Carboxymethylcellulose-Radiesse Voice Gel TM	Fat
Collagen-Cymetra, Zyplast, Zyderm	Fascia
Hyaluronic Acid-Restylane	Polydimethylsiloxane-Bioplastique TM

# Peroral vocal cord injection



# Thyrohyoid vocal cord injection JOHNS HOPKINS MEDICINE



# Unilateral Vocal Cord Paralysis



- Iatrogenic
- Idiopathic
- Neoplastic
- Secondary to medical disease
  
- Recovery if not transected:
  - Full recovery (neuropraxic but no axonal injury)
  - No recovery but adequate compensation
  - Synkinesis

# Early Injection laryngoplasty

- Improve dysphagia and aspiration for inpatients—early discharge from hospital
- Early rehabilitation of voice – why make them wait?
- *Improvement in long term voice outcomes is a new concept—controversial ???*



- Injection laryngoplasty in the acute post operative period is safe and effective in preventing aspiration in patients with VFP following thoracic surgery
  - Graboyes EM et al (2011)
  - Anderson TD et al (2001)
  - Bhattacharyya N et al (2003)
    - Early vs late VF medialization and found statistically significant reduced risk of pneumonia and length of hospital stay for injected patients

# Graboyes et al (2011)

- Retrospective study 20 patients
- Outcomes: 1) safety, effectiveness 2) need for further laryngeal procedures
- Favorable prognosis for RLN or vagal recovery which favors temporary injection medialization.
- The need for further procedures was 25% in the injected group

Time to vocal cord injection	4.5 days
ENT related post operative complications	1 (5%)
Diet recommended pre injection NPO Clear liquid	18 (90%) 1 (5%)
Diet recommend post injection NPO Regular Other oral	1 (5%) 12 (60%) 7 (35%)

# Barbu et al (2015)

- Retrospective study of 68 patients
- Outcome: Feasibility in completion of injection laryngoplasty peroral at bedside in immediate post operative period for glottic insufficiency
- Mean time to bedside injection 8.2 days
- 40 patients were NPO prior to injection
- 70% had advancement to po diet after injection
- Conclusion: feasibility high for peroral bedside injection

# Why early injection laryngoplasty

- Improve glottic insufficiency beyond the expected time for injectate absorption
- Position of vocal cord allows for optimal synkinesis, and long term glottic sufficiency

# Friedman et al (2010)

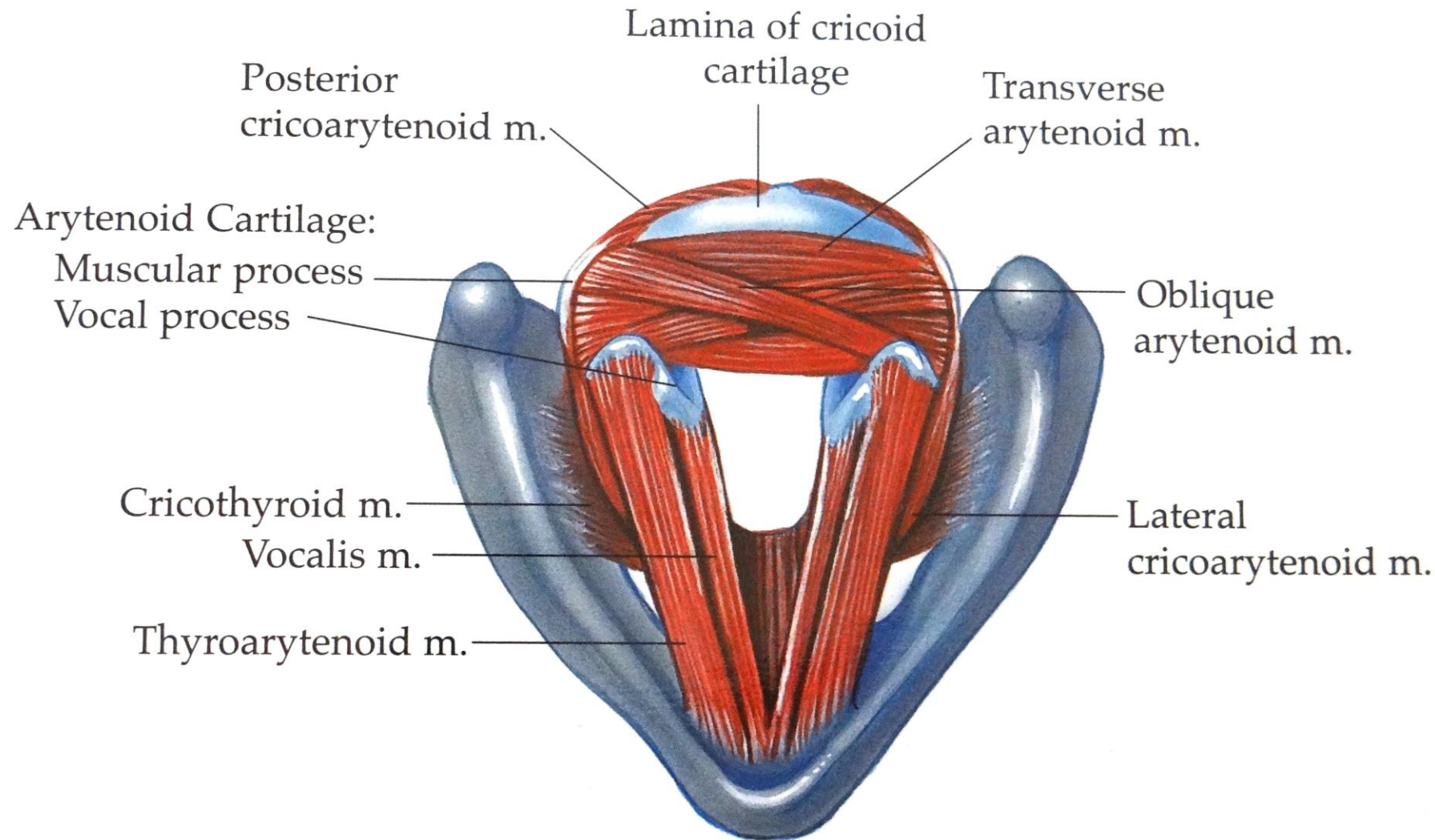
- Retrospective review 35 patients with UVFP
- Objective: Early temporary injection decreases the need for permanent medialization

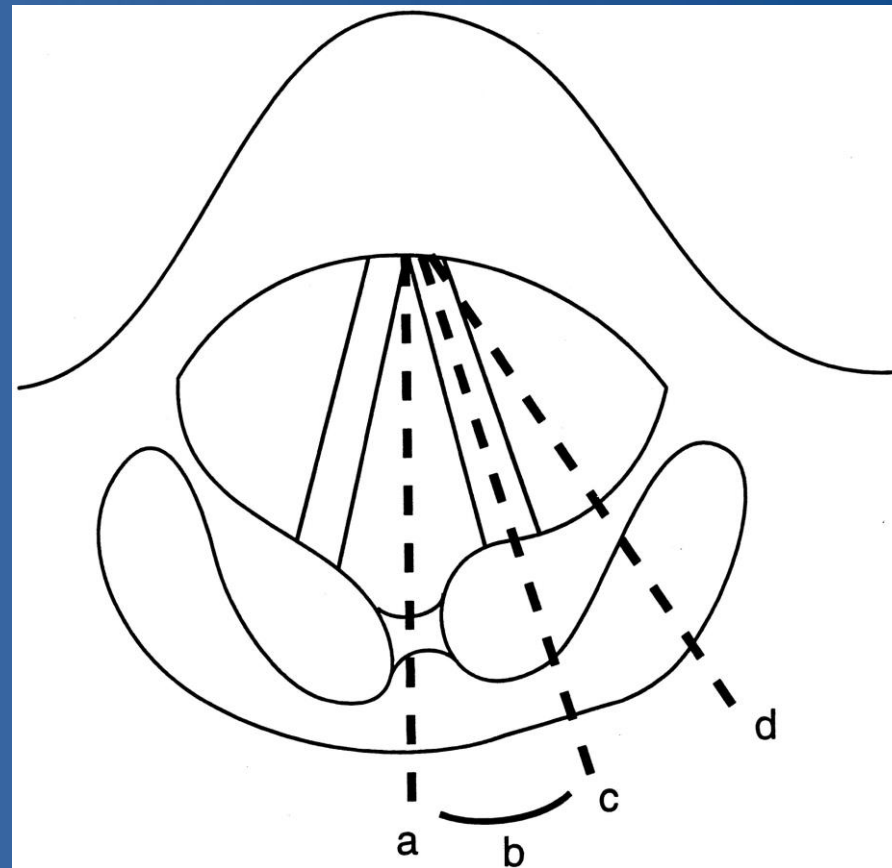
Time to injection	Number	Need for further procedures	Need for framework surgery (permanent)
Injection < 6 months	32	13—2 <sup>nd</sup> injection 4—3 <sup>rd</sup> injection	12
Injection > 6 months	3		3

- Injection < 6 months: near optimal synkinetic recovery given improved position
- Theory: Sensory (vibrotactile) stimulation from physical contact with contralateral cord (rat CN VII, XI studies)
- Theory: Fibrosis of vocal cord secondary to injectate

# Laryngeal synkinesis

- PW Flint et al (1991)
  - Synkinesis: synchronous contraction of muscles that normally do not contract together
  - Antagonistic muscle groups (stronger adductors vs weaker abductors) results in immobility
  - Incidence is 66-88% (experimental)
  - Methods: RLN transected and reanastomosed in rats, followed by injection of retrograde tracers into laryngeal muscles to label motor neurons in the brain stem. Some of the dye injected into the adductors muscles found its way into the brain stem area that supplies the PCA muscle
  - Result of misdirected axonal regeneration and inappropriate reinnervation of abductors by adductor fibers
    - Siribodhi et al: inappropriate EMG activity (dog studies)







# Woodson et al (2007)

- Evaluated synkinesis seen in vagal injuries versus RLN injuries
- Animal model: 15 cats
- Resection of RLN vs vagus
- EMG of TA and PCA pre and post resection (4-6 months after resection of nerve)
- Histologic evaluation of muscles
- RLN regenerated across the gap
- EMG showed activity of TA muscles over PCA of the affected side
- TA affected with inspiration (PCA fibers went to TCA, synkinesis)
- Strong propensity for laryngeal reinnervation after RLN injury but not after vagal injury; this may account for medial position of paralyzed vocal cord

# Yung et al (2011)

- Retrospective review 54 patients

	Injection laryngoplasty (IL)	No intervention
Number (54)	19	35
Second IL with no framework surgery	6	
Framework surgery	5	23

- Mean time of symptom onset to presentation was 39-42 months for both the injection and conservative groups.
- Follow up < 9 months so difficult to know if recovery happened alone
- Selection bias for those with injection medialization (more symptomatic dysphonia received injection versus others)

# Prendes et al (2012)

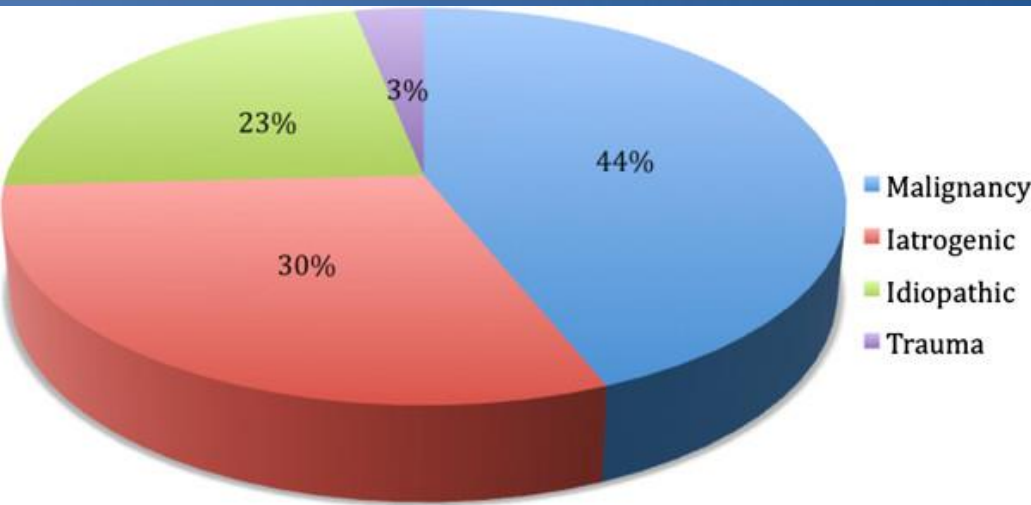
- Retrospective review 38 patients
- Temporary medialization decreased the need for permanent medialization with improvement in laryngeal findings and acoustic measures

	Number	Time to presentation	Framework surgery	Follow up time
IL	14	10.4 mo	4	9.5 mo
CM	24	11.3 mo	18	12.3 mo

- CAPE-V ratings and overall laryngoscopic findings (2 laryngologists) improved in IL group vs CM on follow up
- Rating score system for both CAPE-V and laryngoscopic findings (worse CAPE-V score with those opting for permanent medialization)
- Less permanent medialization for those with IL because of position of vocal cord, synkinesis, vibrotactile feedback and inciting fibrosis

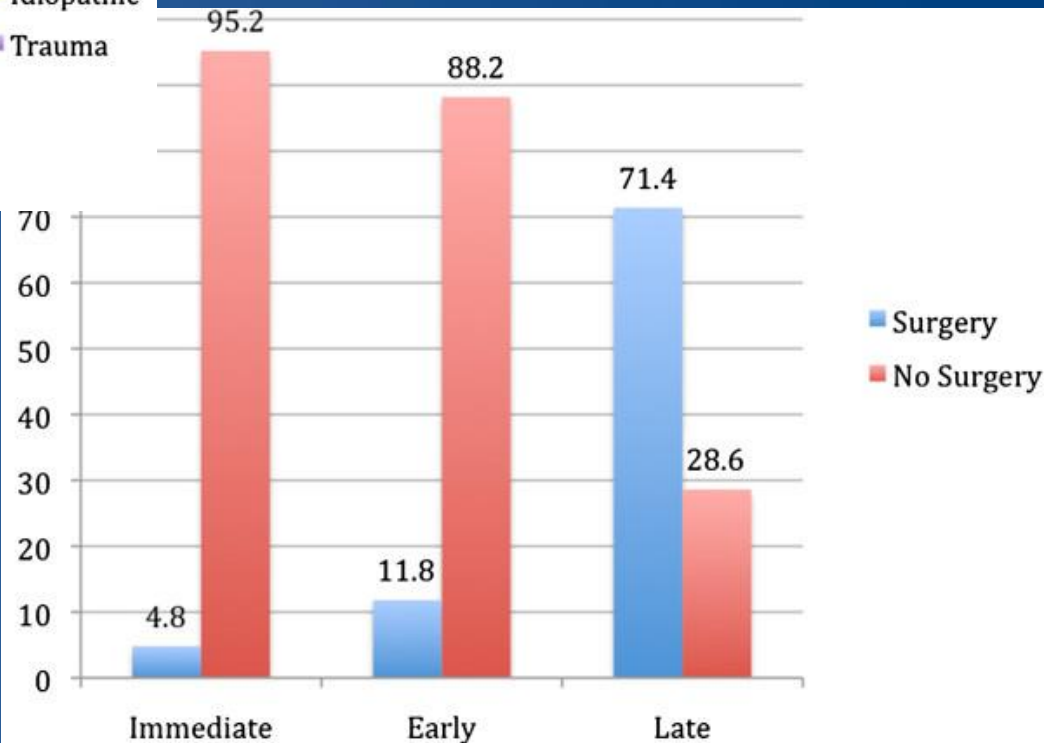
# Alghonaim et al (2013)

- Retrospective study 28 patients
- Objective: to determine whether VFI < 3 months (immediate), 3-6 months (early), > 6 month (late) influences need for framework surgery
- Statistically significant difference between VFI < 3 months compared to > 6 months
- Of the 23 patients who required laryngeal framework surgery, 20/28 were from the late group



Comparison of need for type I thyroplasty at immediate (<3 months), early (3-6 months) versus late (> 6 months) group

Etiology of unilateral vocal cord immobility



# The other side of the story

- Francis et al. Laryngoscope 2015 (Trio thesis paper)
- Overrepresentation of patients with transient paralysis (early presenters) can bias earlier results
- Objectives
  - Retrospective cohort study to investigate whether augmentation reduces likelihood of ultimately need framework surgery
  - Practice patterns in UVP management

- 633 patients with UVFP, divided by etiology
- 41% required intervention in the form of a procedure (132)
- 87% (115/132) injection laryngoplasty (ultimate treatment)
- 17/17 underwent framework surgery first
- 19% (23/115) with injection had framework surgery
- UVFP who underwent IL presented at 4 months vs 7 months
- Those who underwent IL had improved quality of life
- Time to injection augmentation did not effect of odds of ultimately undergoing framework surgery

**TABLE III.**  
**Months from UVFP Symptom Onset to Presentation to Community Otolaryngology and/or Academic Center.**

	Community	Academic Primary*	Academic Secondary <sup>†</sup>	Overall
Symptom Onset to Presentation	2 m [1–5; 1–144]	4 m (2–9; 1–672)	9 m [5–24; 1–576]	6 m (3–15; 1–672)
Symptom Onset to Surgery	Injection	4 m [1–10.5, 1–120]	4.5 m (3–8; 2–109)	6 m [4 –10; 2–433]
	Framework	12 m [6–26; 1–216]	11 m (7–20; 3–433)	16 m [11–33; 2–433]
	Overall	5 m (1–11; 1–216)	6 m (3–11; 2–433)	13 m (7–25; 2–433)

Median months (interquartile range; range).

\*Primary = seen at academic center without prior outside otolaryngology consultation.

<sup>†</sup>Secondary = seen at academic center after outside otolaryngology consultation.

UVFP = unilateral vocal fold paralysis.



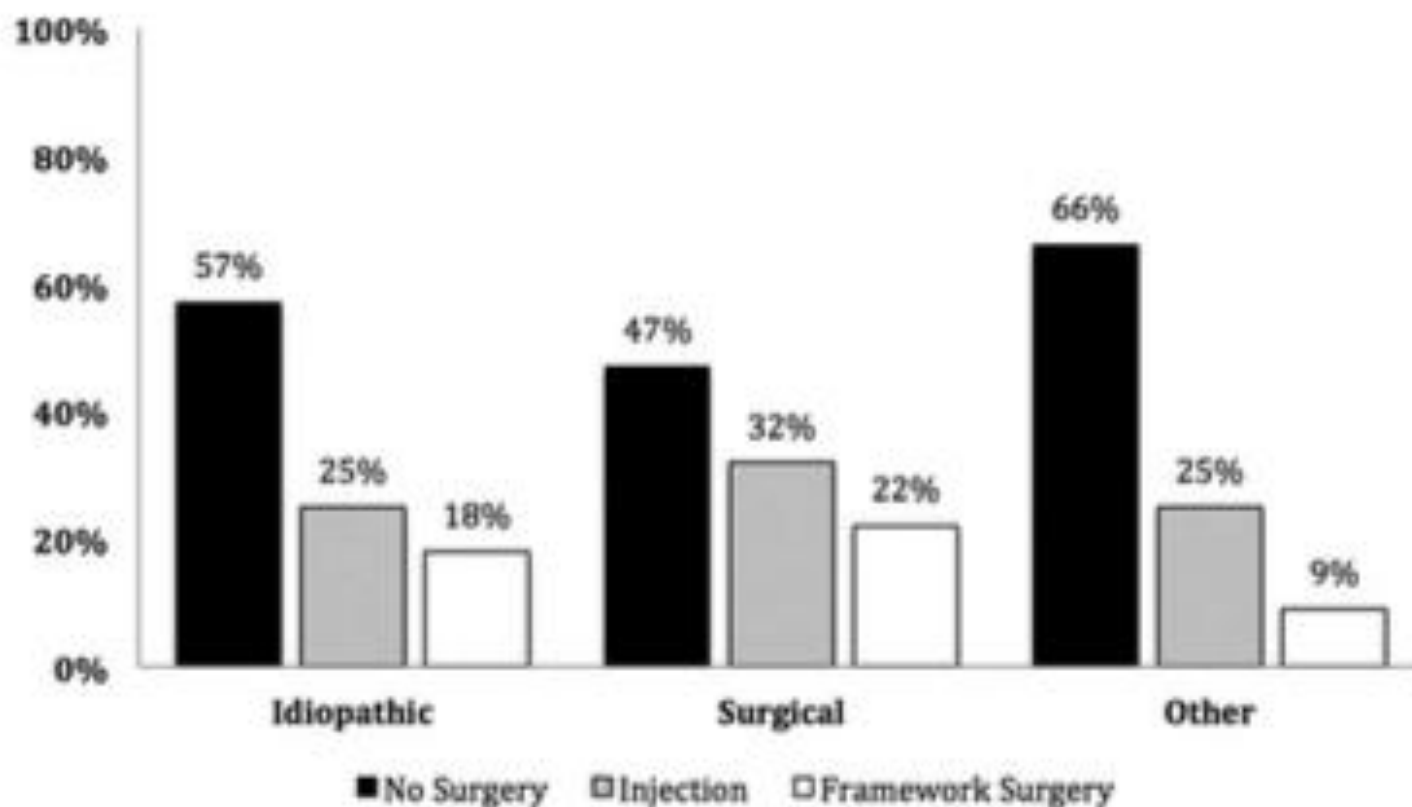


Fig. 2. Ultimate treatment based on etiology of unilateral vocal fold paralysis.

# Need for framework surgery

TABLE IV.  
Comparison of Injected Patients Based on Whether They Ultimately Underwent Framework Surgery.

Characteristics	Framework Surgery		P
	No (N = 92)	Yes (n = 23)	
Age, median (IQR)	61 (51.5–70)	64 (52–71)	0.72
Gender			
Male	55%	56%	0.93
Female	45%	44%	
Etiology			
Nonsurgical	74%	21%	0.08
Surgical	26%	2%	
Complete VF closure*	32%	41%	0.42
Paralysis side			
Right	37%	35%	0.85
Left	63%	65%	
Duration of symptoms, <sup>†</sup> median (IQR)	4 m (2–5)	4 m (2–6)	0.32

VF closure was complete with maximal effort at initial presentation to laryngology.

\*Complete vocal fold closure with maximal effort on flexible laryngoscopy.

<sup>†</sup>Duration of UVFP symptoms prior to treatment.

IQR = interquartile range; VF = vocal fold.

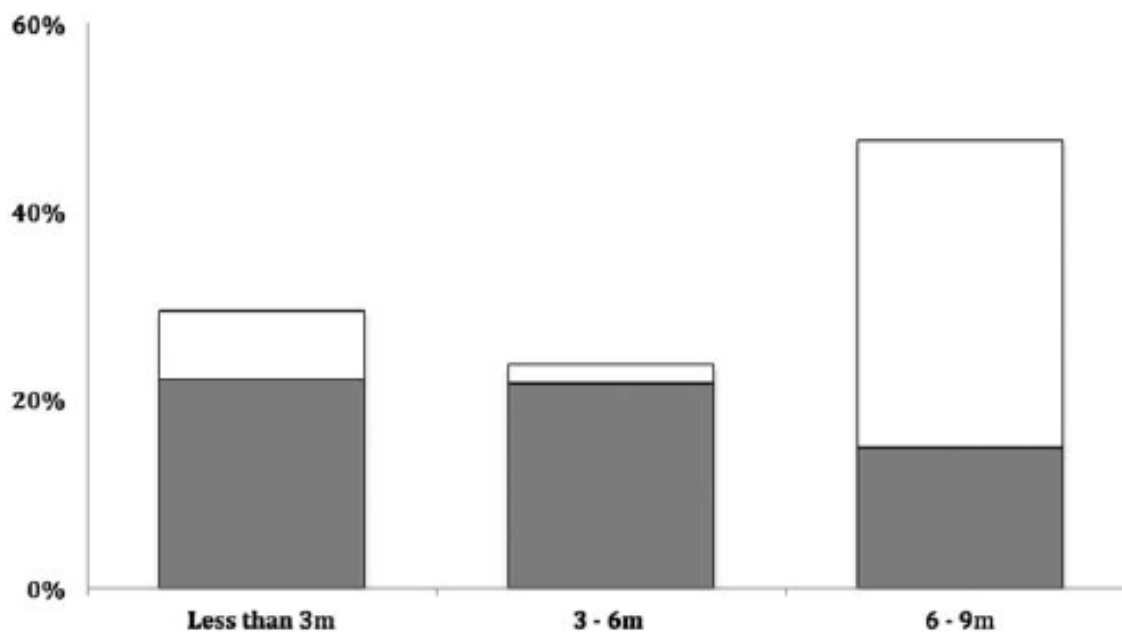


Fig. 3. Percent of patients who had framework surgery with (gray) or without (white) prior injection augmentation based on months from symptom onset to presentation at academic center.

TABLE V.

Multivariate Analysis of Predictors of Framework Surgery Among Patients Who Underwent Injection Augmentation.

Characteristics	Odds Ratio	95% CI	P
Etiology			
Nonsurgical	Reference		
Surgical	4.25	0.90–20.1	0.068
Months before treatment	1.13	0.92–1.40	0.233

CI = confidence interval.

- Evaluation of selection bias
- Francis et al addressed risk of bias using stepwise multivariate analyses whereby time to presentation for treatment is a continuous variable.
  - Compared UVFP seen between 1-6 weeks versus UVFP seen at 6 months
  - UVFP who undergo injection are diagnosed earlier and therefore undergo spontaneous recovery
  - Nearly half of controls with UVFP undergo recovery (no intervention)

# Pei et al (2015)

- Randomized prospective study on 29 patients (14 in injection group; 15 in conservative group)
- Objective: injection does not effect nerve recovery
- Laryngeal EMG, UVFP-related quality of life, acoustic analysis, health related quality of life evaluated at 1,3 and 6 months in injection group; and baseline and 6 months in CM group
- The only statistical significance was in health related quality of life
- The mean disease onset < 6 months (spontaneous recovery)
- No role of hyaluronate injection laryngoplasty in expediting neural recovery, only improving psychosocial quality of life

Table 2  
Changes in measurements between baseline and 6-months follow-up in the two groups

	HI group		CM group		F value	p value
	baseline	6 months	baseline	6 months		
NGGA	10.0 ± 2.1	4.5 ± 1.8	10.7 ± 3.2	5.0 ± 1.6	0.08	0.78
Peak turn frequency						
Lesion side (turn/s) †	261.1 ± 52.4	417.1 ± 113.4	317.9 ± 77.7	551.7 ± 116.3	0.32	0.58
Normal side (turn/s) †	884.7 ± 127.6	837.4 ± 112.4	674.4 ± 81.5	732.6 ± 97.6	0.39	0.54
VOS	34.9 ± 3.5	62.6 ± 4.6	42.1 ± 4.5	70.0 ± 4.7		
Laboratory voice analysis						
Maximum phonation time (s)	3.3 ± 0.6	7.5 ± 1.1	5.9 ± 1.0	11.7 ± 1.9	0.65	0.43
SZ ratio	3.0 ± 0.5	1.5 ± 0.2	3.2 ± 1.3	1.2 ± 0.1	0.09	0.77
Fundamental frequency (Hz)	171 ± 14.7	175 ± 12	181.5 ± 9.1	193 ± 17	0.32	0.58
Jitter (%)	3.3 ± 0.9	1.7 ± 0.3	2.9 ± 0.4	2.1 ± 0.4	0.68	0.42
Shimmer (dB)	1.0 ± 0.2	0.8 ± 0.2	1.4 ± 0.3	1.4 ± 0.3	0.26	0.62
Harmonic-to-noise ratio (dB)	1.9 ± 1.3	8.8 ± 1.0	2.6 ± 2.2	6.3 ± 1.1	0.70	0.41
Quality of life						
Vitality	47.9 ± 7.0	61.0 ± 3.1	57.7 ± 7.0	64.2 ± 5.5	0.67	0.42
Physical functioning	73.6 ± 5.8	81.8 ± 5.9	88.1 ± 3.8	90.4 ± 3.6	0.50	0.49
Bodily pain	78.4 ± 6.4	84.6 ± 5.4	83.2 ± 7.5	87.5 ± 5.6	0.05	0.82
General health perceptions	46.4 ± 7.8	56.4 ± 6.4	55.8 ± 5.3	65.8 ± 5.7	0	1.0
Physical role functioning	26.8 ± 11.3	57.1 ± 12.4	44.2 ± 13.9	84.6 ± 8.3	0.23	0.64
Emotional role functioning	47.6 ± 13.4	90.5 ± 7.4	79.5 ± 11.0	82.1 ± 10.4	4.94	0.36
Social role functioning	47.4 ± 8.0	79.5 ± 5.7	65.5 ± 8.3	76.0 ± 7.3	3.78	0.06
Mental health	50.6 ± 6.2	71.7 ± 5.5	63.4 ± 6.9	68.0 ± 5.1	5.75	0.02*

Data presented as mean ± standard error of mean, \* $p < 0.05$ , † $n = 10/8$  in HI/CM groups, respectively. HI hyaluronate injection, CM conservative management.

# Questions to ask

- Is there really a decrease in framework surgery for those who receive early injection? What timeframe accounts for early injection?
- What is the role of synkinesis? When is the timeframe for synkinesis expected to happen?



# Conclusion

- No prospective study has been performed:
  - Comparing conservative management to early injection (versus late injection)
  - Endpoint: need for ultimate framework surgery
  - Endpoint: vocal cord motion recovery versus voice recovery
- Follow up of patients with UVFP must be at least 9-12 months
- Suggested selection bias
- Role of early injection laryngoplasty for quality of life in patients

