Laryngeal Injectables: A Review of Vocal Fold Augmentation Materials

Available substances
- 1960-1978 1
- 1978-1986 2
- 1986-1996 3
- 1996-2009 10+

WHICH Laryngeal Injectables should I use and WHEN?

Understanding Glottal Insufficiency
- Failure of the vocal folds to close adequately during vibration
- Etiology
  1. Inability of to place vocal folds into the required prephonatory position
     - Loss of neurologic activity – Paralysis/Paresis
     - Scaring of joint
  2. Loss of mucosal surface – does not allow Bernoulli effect to create closure
**Physiology of Glottic Closure**

1. Intrinsic laryngeal musculature brings the vibratory membranes into a nearly closed configuration
   - Vocal fold vibratory cycle begins with the vocal folds slightly apart
   - Titze & Verdolini

2. Mucosal membrane pliability
   - Air movement through the glottis creates a vacuum and sucks supple vocal fold mucosa together

**Glottal Insufficiency - Etiology**

1. Motion impairment
   - The paralyzed vocal fold rests between the phonatory position and the respiratory position
     - Horizontal
     - Vertical

2. Disorders of vocal fold mucosa
   - “Vibratory Membranes are no longer pliable and cannot be drawn together by Bernoulli forces”
     1. Scaring
     2. Sulcus Vocalis
Injection Laryngoplasty for Unilateral Vocal Fold Paralysis

- Historically - Injection into paraglottic space for the management of unilateral paralysis – “…to restore the ability to laugh.”

- Material placed laterally in the vocal fold because it was recognized that a foreign body reaction occurred against the substance
  - Procedure was resurrected in the 1960’s with Teflon Paste, but considered difficult by Arnold, Montgomery and Dedo
    - Limited number of centers

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Injection Laryngoplasty for Paresis and Mucosal Surface Loss


- Problems
  - Injected material creates inflammation
  - Injected material too stiff to vibrate

Problems – Technical Difficulties

- Difficult surgical technique
  1. Position - How deep to place the needle
  2. Once substance leaves needle it will flow through the path of least resistance into a resting position
  3. How much substance to add

Sea Change X 2

1. Available substances
   - 1960-1978 1
   - 1978-1986 2
   - 1986-1996 3
   - 1996-2009 10+

2. Injection indications
   Transformation from treating paralysis with injection to treating all forms of GI with injection

How Deep to Place the Needle

 Placement of Substance

- Traditional placement
- Early proposed placement for collagen substance

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**Position of Needle and Placement of Substance**

- Influenced by size of needle used to inject
- Size of needle is determined by choice of substance
  - Fat
    - 18 or 19 g needle required for viability of cells
  - Teflon 19 g needle
  - Collagen compounds
    - 23 to 27 g needle
  - Calcium Hydroxylapatite
    - 25 to 27 g needle

**Potential Resting Positions for Injected Substances**

- Within TA Muscle
  - Lateral
  - Intermediate
  - Medial

- Within Vocal Ligament
  - Just Deep to the Ligament
  - Reinke’s Space
Potential Resting Positions for Injected Substances
Outside of Larynx

Vocal Fold Height

<table>
<thead>
<tr>
<th></th>
<th>FEMALE</th>
<th>MALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Mean (mm)</td>
<td>7.5</td>
<td>8.6</td>
</tr>
<tr>
<td>SD</td>
<td>0.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

● Extrusion in Female Larynx
  - Lateral injection of greater than 0.4 ml of substance

Extruded
Approaching
Non-Extruded

Extrusion vs. Non-Extrusion

Favorable Resting Positions for Injected Substances

Substance Follows Path of Least Resistance after Injection
Pattern of Deposit

Medial
Intermediate
Lateral

Multilobular distribution
Volume Required (mL)
Cadaver Experiments

<table>
<thead>
<tr>
<th></th>
<th>Medial TA Injection</th>
<th>Lateral TA Injection</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.14 +/- 0.07</td>
<td>0.41 +/- 0.19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.23 +/- 0.09</td>
<td>0.62 +/- 0.18</td>
<td>&lt; 0.001</td>
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</tbody>
</table>

Problems Related to Choice of Substance

- Viscosity mismatch between the injected substance and the normal lamina propria
  - Chan and Titze
- Host reaction to the substance
  - Inflammation and granuloma formation with potential airway obstruction
  - Stiffening of vibratory cover

Laundry List of Available Substances

- Temporary (2-5 mos)
  - Gelfoam
  - Radiesse Voice Gel
  - Novielle Gel
  - Collagen Products
    - Zyplast (bovine)
    - Cosmoplast (human)
    - Cosmoderm (human)
    - Cymetra
  - Hyaluronic Acid Gels
    - Restylane, Perlane
      - Rooster Combs
    - Hyalan, Hyalan Plus
      - Bacterial fermentation

- Long-term/Permanent
  - Autologous fat/fascia
  - Radiesse (CaHA) ?
  - Novielle Gel Plus ?
  - Teflon
    - Limited role
Gelfoam

- Gelatin
  - Bovine gelatin
  - Sterile powder (1 gm)
- Longest track-record of laryngeal injectables
  - 30+ years
- #1 injectable substance
  - ABEA survey, 2004 (Merati)
- Results
  - Short acting (6 weeks)
  - Must use 18g needle for injection
  - Limited use in modern day practice

Collagen-Based Injectables

- Zyplast
  - Longest track record (20+ yrs)
  - Least expensive
  - Bovine-derived
  - Immunogenicity / Skin testing recommended
- Cymetra
  - Micronized cadaveric dermis
  - No skin testing
  - Prep. Required
- Cosmoplast/Cosmoderm
  - Human engineered collagen
  - No skin testing
  - No track record

Collagen-Based Injectables

<table>
<thead>
<tr>
<th>Product</th>
<th>Yrs.</th>
<th>Material</th>
<th>Length of effect</th>
<th>Pros</th>
<th>Cons</th>
<th>g</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zyplast/Collagen</td>
<td>20+</td>
<td>Bovine collagen</td>
<td>4-6 mos</td>
<td>Long track record</td>
<td>Allergy Delay</td>
<td>27</td>
<td>$165</td>
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<tr>
<td>Cymetra</td>
<td>4+</td>
<td>Cadaveric Dermis</td>
<td>2-4 mos</td>
<td>No allergy</td>
<td>Prep time Unpredict.</td>
<td>25-27</td>
<td>$250</td>
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<tr>
<td>Cosmoplast/Cosmoderm</td>
<td>&lt;1</td>
<td>Human-engineered</td>
<td>?</td>
<td>No allergy</td>
<td>No track record</td>
<td>27</td>
<td>$235-$205</td>
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</tbody>
</table>
## Hyaluronic Acid

- Introduced as an injectable in Europe 1996
- Used in Facial Plastics to fill wrinkles (FDA clearance 2004)
- Naturally occurring Glycosaminoglycan (polysaccharide) within the dermis or LAMINA PROPRIA
  - Functions to control tissue viscosity by binding water
  - Produced in response to injury
- Produced from 2 sources
  - Avian protein
  - Recombinant forms

## Injectable Hyalan Gels

<table>
<thead>
<tr>
<th>Product</th>
<th>Source</th>
<th>Rheologic Properties</th>
<th>Particle size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hylaform</td>
<td>Rooster combs</td>
<td>Elastic</td>
<td>200-700µ</td>
</tr>
<tr>
<td>*Perlane</td>
<td>Bacterial fermentation</td>
<td>Viscous</td>
<td>100 µ</td>
</tr>
<tr>
<td>Restylane</td>
<td>&quot;</td>
<td>&quot;</td>
<td>40-60µ</td>
</tr>
<tr>
<td>Restylane Fine Lines</td>
<td>&quot;</td>
<td>&quot;</td>
<td>20-30µ</td>
</tr>
</tbody>
</table>

* = not available in USA

## Hyalan Gels

- Longevity
  - Reported as 4 to 6 months
  - Personal experience is 2 to 4 weeks
- Low tissue reactivity
  - Sugar
  - No antigenic qualities
  - Low level of protein impurities
  - Hypersensitivity 0.6%

## Radiesse Voice Gel

- Carbomethylcellulose
  - Wood-based
  - No allergy
  - Gel carrier substance in Radiesse
- Shorter duration (2-3 months)
- FDA-approved for use in larynx
**Radiesse Voice Gel™**

- Packaged with needles for injection
- No pre-treatment
  - e.g. mixing, warming, loading... “Off the shelf use”
- Results
  - Easy to inject
  - Well tolerated
  - Minimal inflammatory reaction
  - Longevity 2 to 6 months

**Novielle Gel™**

- Patent protected material
  - Uncertain of contents
- Intended to be temporary and manufacturer is working to produce substance with known resorption rate
- Minimal experience (n = 2)
  - 1 early resorption
  - 1 misplaced into LP and needed surgical removal due to lack of resorption at 3 months

**Glottic Injectables:**

- **Long-lasting substances**
  - Teflon
  - Autologous fat and fascia
  - Radiesse™
  - Novielle Gel Plus™
Teflon®

- Designed for the management of unilateral paralysis
- Ford reported poor outcomes when injected into mobile vocal folds
- Reasons for poor outcomes
  - Viscosity mismatch
  - Poor placement
  - Migration
  - Giant cell foreign body reaction
    - Teflon® Granuloma

Lipoinjection

1. Preparation can be troublesome
2. Length of response is unpredictable
3. Need for over injection

Calcium Hydroxylapatite (CaHA)

- Found naturally in Bone and Teeth
  - Mineral Component
- Used as solid implant for 20 years
  - Dentistry
  - Orthopedics
  - Maxillofacial Reconstruction
- Well tolerated as biologic implant

OVER INJECTION REQUIRED
**Radiesse™**

- Spherules of Calcium Hydroxylapatite
- Suspended in aqueous gel
  - Water, glycerin, carbomethylcellulose (CMC)
- 25-45 microns in diameter
  - Can pass through 27 gauge needle or larger
- Forms a “scaffolding” for tissue in-growth
- FDA Approved for Vocal Fold Augmentation

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**CaHydroxylapatite - histology**

12 months (40x)

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**Radiesse™ Special Considerations**

- Material flows better if slightly warmed
- Requires moderate hand pressure at start of injection
- Slight Overinjection (5-10%) is required to adjust for the lost of the carrier material
- Temporary VF stiffness for 1-2 months following injection, worse if injection is placed superficially

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**Radiesse™ Indications/Duration**

- Permanent augmentation of the vocal fold
  - Paralysis
  - Paresis
  - Atrophy
    - NOT SCAR
- Duration
  - 1 to 2 years clinical experience
  - Bioform reports up to two years, but unknown

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OHNS Website: http://ohns.ucsf.edu
Novielle Gel Plus™

- Patented carrier substance plus CaHA
- Newly available
- Minimal clinical experience

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Conclusions

- Understand physiology of glottic closure
  - Vocal folds need to be placed in a nearly closed prephonatory position
  - Mucosal surface must be supple
- Determine why you are injecting
  - Motion impairment
  - Loss of vibratory cover
- Know the characteristic of substance you are injecting
  - Host reaction
  - Longevity may be affected by position
  - Needle size required for injection
- Understand your ability to vary the placement of the substance in the vocal fold