Introduction
Injection laryngoplasty is a surgical procedure used to treat glottal insufficiency. Glottal insufficiency is a condition whereby patients suffer from weak and breathy voice due to air escape through incompletely opposed vocal cords. Injection laryngoplasty is aimed at medializing the vocal cords to aid voice production by opposing the gap. Since its first description in 1911 by Bruening, injection laryngoplasty has evolved in its approaches and materials. It has also gained popularity in recent years owing to its low procedural cost, avoidance of general anaesthesia, technical feasibility and good efficacy. In this review article, we aim to provide a sequential discussion of indication, patient selection, injection materials, technique as well as recent development in this field.

Indication, Contraindications and Patient selection
Injection laryngoplasty is indicated in conditions that lead to vocal cord paresis or paralysis, vocal cord atrophy, vocal cord bowing and vocal cord scarring. These conditions include infection, laryngopharyngeal reflux, tumour, thyroid disease, voice abuse, alcohol abuse, parkinson’s disease, radiotherapy, as well as iatrogenic causes such as recurrent laryngeal nerve injury following surgery. As with this wide variety of etiologies, it is essential that patients are fully examined, investigated and treated for the underlying causes prior to consideration for injection laryngoplasty.

There are clinical situations whereby injection laryngoplasty is considered advantageous:

1. Patients with small glottic gap, from 1–3mm.
2. Patients who cannot undergo general anaesthesia due to multiple co-morbidities. Studies have shown that injection laryngoplasty under local anaesthesia gives comparable results to those who undergo the procedure under general anaesthesia. In fact, local anaesthesia gives the advantage of having a real-time assessment of the patient’s voice during the procedure.
3. Patients with terminal illness whereby general anaesthesia and open procedure would be risky. Studies have shown that injection laryngoplasty under local anaesthesia is safe to perform in this group of patients and improves overall quality of life.
4. Patients with previous neck surgery or irradiated neck, as other surgical options such as Type I thyroplasty or nerve reinnervation may not be feasible.
5. Patients whereby there is a possibility of full functional recovery. Given that injection laryngoplasty is mostly a temporary procedure, it would obviate the need for a reversal or removal of the injected material. In an investigation of long term outcomes of patients with injection laryngoplasty by Arviso et al, patients who ultimately had full recovery of their vocal cord paralysis benefited from injection laryngoplasty as an interim intervention, showing marked improvement in voice-related quality of life scores.
6. Patients who had previous laryngeal framework surgery requiring fine tuning of their voice function. Umeno et al found patients who underwent arytenoid adduction are more likely have increased vocal cord bowing compared to those who underwent thyroplasty. The use of injection laryngoplasty in these patients helped improved their voice function.
There are scenarios where patients would be better served by a different procedure. For instance, patients with large glottic gap or involvement of arytenoids would achieve better results from thyroplasty or arytenoids adduction. In addition, patients with glottic insufficiency caused by an irreversible etiology would benefit more from a more permanent procedure such as thyroplasty. There are no absolute contraindications for this procedure. However, the procedure would be less desirable in anxious patients who are unable to tolerate flexible nasoendoscopy and injection under local anaesthesia. Injection laryngoplasty is not contraindicated in patients taking anticoagulants. In a case series by Luu et al, 59 patients underwent injection laryngoplasty whilst on warfarin without any complications. However, as a precaution, it is the practice of the senior author to withhold anticoagulants for a period prior the procedure to avoid excessive bleeding leading to airway obstruction or aspiration pneumonia. Allergies to injection materials used in the procedure do not prohibit patients from having the procedure itself as there is a wide array of other materials available for use. However, the clinician needs to be aware of such allergy and pre-counsel the patients about the pros and cons of the other injection material used.

Review of materials
The ideal injection material should be

1. Biocompatible, inert and does not cause local tissue reaction or fibrosis
2. Easy to prepare and easy to use. The injection material should be readily available, easy to measure in quantity and easy to inject through a small needle
3. Low cost
4. Is durable, and resistant to resorption or migration
5. Maintains the visco-elasticity of the vocal cord post-injection

The fact is there is no perfect injection material that meets all the criteria above. We classify the injection materials based on its longevity (Table 1) and discuss each of its merits and drawbacks.

<table>
<thead>
<tr>
<th>Injection materials used in injection laryngoplasty</th>
<th>Short term</th>
<th>Longer Lasting</th>
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<tbody>
<tr>
<td>Gelfoam™</td>
<td>Calcium Hydroxyapatite</td>
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<tr>
<td>Radiesse Voice Gel™</td>
<td>Fat</td>
<td></td>
</tr>
<tr>
<td>Collagen - Cymetra, Zyplast, Zyderm</td>
<td>Fascia</td>
<td></td>
</tr>
<tr>
<td>Hyaluronic Acid – Restylane</td>
<td>Polydimethylsiloxane – Bioplastique™</td>
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Gelfoam™
Gelfoam is a substance prepared from purified bovine gelatin. It is supplied as sterile powder requires pre-mixing with saline into a viscous paste for injection. Gelfoam has the longest track-record of uncomplicated use amongst all injection materials and is the most used injectable substance according to a survey by American Broncho-ESOPHAGOLICAL Association in 2006. Gelfoam causes minimal tissue reaction but is also prone to resorption. It last for 4 – 10 weeks and is generally a good means of temporary medialization. It is therefore ideal in clinical scenarios whereby there is a chance of recovery of the vocal fold paralysis, or in situations whereby the definitive procedure has to be delayed. Anderson et al found use in Gelfoam to decrease the risk of aspiration by medializing vocal cords in patients with acute vocal cord paralysis suffering from aspiration. However, Gelfoam has the drawback of requiring an 18 gauge large bore needle for injection, which can be uncomfortable especially for patients undergoing local anaesthesia. It is therefore superseded by newer injection materials which are more convenient to use and have better longevity.

Radiesse Voice Gel™
Radiesse Voice Gel was developed from a gel carrier substance for calcium hydroxylapatite, a longer term injection material. It is composed of sodium carboxymethylcellulose, glycerin and water. It has the benefit of being ‘off-the-shelf’ use, without any need for preparation or harvesting of the injection material. Its inert nature means that it also has the benefit of not requiring any prior allergic testing. It has also been found to give better mucosal vibratory activity post-injection compared to Gelfoam. It can last 1 – 3 months. It can be injected via a 25 to 27 gauge needle, which is easily tolerated by patients. In addition to its routine use in the transcutaneous approach. It can be easily modified for transoral or microaryngoscopic injection.

Collagen derived products
There are a variety of collagen derived products engineered from either bovine or human collagen available for injection. Zyplast and Zyderm are derived from bovine collagen and have been shown to last up to 4 months. There is a 2% risk of allergic reaction, hence the US Food and Drug Administration (FDA) recommends allergy testing prior to usage of bovine collagen injection products, which could lead to delay in treatment. However, in a study by Luu et al, 845 patients did not have prior allergic testing and did not suffer any allergic reactions following injection laryngoplasty with bovine collagen.

Cymetra, Cosmoplast, and Cosmoderm are human based collagen products. Cymetra is derived from human cadaveric dermal tissue and hence poses the risk of infection transmission. However, no such cases have been reported to date. Cymetra has been shown to last ranging from an average 2 – 3 months to more than 1 year. Cymetra injection laryngoplasty has been demonstrating good results in terms of glottic closure, voice quality and voice related quality of life in patients. In a large case series on Cymetra by Tan et al, over-injection is required to account for the likely resorption. Resorption has also been noted in other case series. However, owing to its good safety profile, repeat injections are usually non-problematic. In the case series by Tan et al, of the 159 patients on long term follow up, 14% required repeat injection, and about 20% subsequently required open procedures.

Cosmoplast and cosmoderm are engineered purified human collagen. Both have more reputation as dermal fillers and fewer track records in laryngeal use. However, because it is engineered and purified in the laboratory, there is less risk of infection transmission.

Hyaluronic Acid
Hyaluronic acid is a natural polysaccharide that is part of the extracellular matrix, which is also found in the lamina propria
of vocal cords. It aids the repair and tissue regeneration in vocal cords by providing synthetic building blocks for the extracellular matrix.\textsuperscript{25, 26, 27} Rheologic studies have shown that Hyaluronic acid-based injection materials have viscoelastic properties that best resemble that of a human vocal fold.\textsuperscript{28} It has low tissue reactivity and therefore has a good safety profile\textsuperscript{29, 30} despite the anecdotal report of granulomatous tissue reaction.\textsuperscript{31} Commercially available preparations such as Restylane and Hylan b Gel are made of cross-linked chains of hyaluronic acid, forming a viscous gel. It generally lasts about 4 – 6 months.\textsuperscript{20, 21} However, some studies have shown that it can last up to 12 months.\textsuperscript{29, 30} It certainly has been found to have a longer duration compared to bovine collagen in a study done by Hertegard \textit{et al}\.\textsuperscript{32} In animal studies done by Dalqvist \textit{et al}, hyaluronic acid was found to be advantageous over Teflon and collagen products as they give post-injection results showing visco-elasticity of the vocal cords mimicking that of the control vocal fold tissue.\textsuperscript{32} However, clinical use has been found to be less than satisfactory.\textsuperscript{20, 21}

**Autologous fat injection**

Autologous fat injection has a longer lasting effect compared to other materials above. It has been shown to provide long term improvement of voice function comparable to thyroplasty.\textsuperscript{33} Its effect has been shown to last 26 months and more.\textsuperscript{34, 35} However, the actual duration is variable as the rate of resorption is unpredictable. Fat tissues are harvested in theatre, typically from subcutaneous tissues in the abdominal wall. Its autologous nature makes it biocompatible and safe for use.\textsuperscript{36, 37} It is also one of the materials that maintain the visco-elasticity of the vocal fold post injection.\textsuperscript{38} The disadvantage of fat injection is the prolonged harvest time and variability in its results due to unpredictable fat survival. Complication rate is low although there have been reports of donor site haematoma,\textsuperscript{36, 37} poor voice quality due to over-injection\textsuperscript{39} and fat extrusion.\textsuperscript{36, 37, 38} In addition, patients will have to undergo general anaesthesia. Patients also tend to suffer prolonged post-operative dysphonia up to a few weeks, owing to the necessary over-injection. There has been a recent development in using autologous fat in combination with fascia for injection laryngoplasty. The rational being that fascia helps with regeneration within the vocal fold whereas fat maintains the pliability of the vocal cords. Studies by Cheng \textit{et al} using this combination have shown sustained volume of injection up to 24 months post-injection, voice improvement and adequate mucosal vibration.\textsuperscript{40}

**Autologous fascia**

Autologous fascia was introduced by Rikhanen in 1998 with the advantage of low metabolic requirements, more stability and less prone to resorption compared to autologous fat or collagen.\textsuperscript{41} Fascia can be harvested from fascia lata, temporal fascia, rectus abdominis sheath or aponeurosis of the anterior abdominal wall. Fascia lata is the preferred donor site owing to the abundance of tissue and easy access.\textsuperscript{42} Fascia is harvested, minced and injected into the paraglottic area. Autologous fascia has the advantage of being inexpensive and abundantly available. It also has minimal of risk of rejection, allergic reaction or infection transmission. Studies have also demonstrated that voice analysis post-injection is improved compared to pre-operative state.\textsuperscript{41, 43, 44} Post-injection videostroboscopic assessment by Rikhanen \textit{et al} showed symmetry in amplitude and synchrony in phase of the vocal cord mucosal wave in majority of the study subjects.\textsuperscript{45} In the same study, it was noted that there was no scarring or fibrosis of the subepithelial space following fascia injection.\textsuperscript{45} Recent study by Reijonen \textit{et al} showed that the post-injection results can last ranging from 3 – 10 years.\textsuperscript{46} The same study also concluded that autologous fascia injection laryngoplasty is more suited for patients with smaller glottic gap.\textsuperscript{47} The slight drawback of autologous fascia is its risks of donor site morbidities.

**Calcium Hydroxyapatite (CaHA)**

Calcium Hydroxyapatite is a type of mineral found in human bone and teeth. Its injectable form consists of microspheres of calcium hydroxyapatite suspended in carboxymethylcellulose carrier gel. It is easily injected via a 25 – 27 gauge needle. It has stellar reputation in dental use and as dermal fillers in reconstructive surgery. Radiesse Voice\textsuperscript{34} is the commercial preparation used in injection laryngoplasty and has the benefit of ‘off-the-shelf’ use. Rees \textit{et al} has demonstrated that calcium hydroxyapatite injection can be safely performed in an office setting to produce good results.\textsuperscript{47} Other studies have also concurred.\textsuperscript{48, 49} Karagama \textit{et al} reported significant improvement in voice quality following CaHA injection medialization in a group of palliative patients.\textsuperscript{7} Studies by Kwon \textit{et al} and Rosen \textit{et al} found that calcium hydroxyapatite injection laryngoplasty showed sustained improvement of voice up to 12 months.\textsuperscript{38, 39} Longer term study by Carroll \textit{et al} showed that CaHA has longevity up to 24 months post injection, with deterioration of voice quality after 24 months.\textsuperscript{50} There has been an interesting animal study by Ozdagrou \textit{et al} which found neocartilage formation in the vocal fold following injection with CaHA.\textsuperscript{51} This could possibly explain the longevity of CaHA. However, it is yet unknown that whether human larynx would react similarly. In addition, the impact of this neocartilage formation on the visco-elasticity of the vocal fold is unknown.

Both animal and human studies have concluded that over-injection is required to account for the resorption of the carrier gel substance.\textsuperscript{31, 34} However, the histologic examination in the animal study confirmed that there was no resorption or migration of the CaHA.\textsuperscript{54} Although CaHA is a naturally occurring mineral in the human body and should therefore be biocompatible, there has been a case report on giant-cell foreign body reaction to CaHA.\textsuperscript{55}

**Polydimethylsiloxane (PDMS)**

Polydimethylsiloxane is a silicone-based organic polymer renowned for its rheologic properties, making it suitable for vocal cord medialization. In a study by Bergamini \textit{et al}, patients who underwent injection medialisation with PDMS showed sustained acoustic and aerodynamics improvement on a median follow up of 21.7 months.\textsuperscript{56} Turner \textit{et al} reported that patients have improved swallowing and improved Voice Handicapped Index following injection laryngoplasty with PDMS.\textsuperscript{57} Hamilton \textit{et al} compared patients post PDMS injection to patients who underwent Isshiki’s thyroplasty and found that both groups produce similar improvement in voice performance, with fewer complications in the PDMS group.\textsuperscript{58} However, there have been several reports of granulomatous reaction, extrusion and migration of PDMS following injection into vocal fold.\textsuperscript{59, 60, 61, 62} This has been a similar occurrence with the use of PDMS in other body sites.\textsuperscript{63, 64} This suggests that although the risks are low, use of PDMS is not without complications.
**Injection Laryngoplasty**

**Figure 1:** Video monitor connected to flexible nasoendoscope to help display injection site

**Figure 2:** Equipments required for injection (1) Packaging of Radiesse Voice, (2) 25cm 25G laryngeal injection needle, (3) Radiesse voice syringe, (4) Nozzle for local anaesthetic drops in the larynx, (5) pack for the nozzle, (6)Lidocaine 5%/phenylephrine 0.5% spray, (7)Xylocaine 10mg spray, (8) 4% lignocaine for laryngeal anaesthesia
Injection Laryngoplasty

Other materials

Earlier injectable materials such as paraffin and Teflon have been gradually phased out due to various inflammatory and foreign body reactions, as well as high extrusion rates. Teflon has in particular been associated with risk of granuloma formation.65, 66, 67

Equipment and preparation

Injection laryngoplasty can be performed either in operating theatre or in the clinic setting. With regards to performing injection laryngoplasty in the clinic, the authors recommend the use of Guidelines for development of a Laryngeal Intervention Clinic (LInC).68

Adequate preparation is essential. Patient should be counseled with regards to procedure and consent obtained. Patient can be positioned sitting upright in a chair or lying flat with neck slightly extended to allow access to the neck and larynx. Equipment (Table 2) should be set up prior to patient entering the room.

Technique

There are 3 approaches to injection laryngoplasty - transcutaneous, transoral and microlaryngoscopic injection. The description of techniques below is based on the use of Radiesse Voice which is the material of choice of the senior author.

Transcutaneous injection

Transcutaneous approach can be further divided into cricothyroid, thyrohyoid and transcartilaginous approach, depending on the site of injection. Adequate local anaesthesia is crucial. This involves infiltrating the overlying skin with 2% lidocaine and anaesthetising the nasal and pharyngolaryngeal cavity with xylocaine spray. Flexible nasoendoscope is passed by the assistant to visualize the vocal cord and paraglottic area.

Cricothyroid approach

Cricothyroid approach is the commonest approach. Needle and syringe containing the injection material is inserted at the cricothyroid notch and advanced through the cricothyroid membrane supero-laterally into the paraglottic area. The injection material is then injected until a desired position of the vocal fold is achieved. Patient should be kept nil by mouth for an hour and if procedure was performed in the clinic setting, patient should be observed for 1 hour prior to discharge. In our practice, we review the patients at 1, 3, 6 and 12 months post injection. Patients are also informed that a re-injection or thyroplasty may be necessary in the future. The cricothyroid approach has disadvantages in that the anatomical landmark may not always be readily identifiable especially in obese patients and in patients with previous neck surgery. In addition, it can sometimes be difficult to gauge the depth and location of needle tip due to the oblique direction of injection.69

Thyrohyoid approach

The trans-thyrohyoid approach involves inserting the needle above the thyroid cartilage through the thyrohyoid membrane, with the needle directed inferiorly towards the paraglottic space for injection. This approach is advantageous in that it allows needle placement under direct visualization.69,70 However, it also has the disadvantage of leakage of injection material from the needle puncture site.

Transcartilaginous approach

Transcartilaginous approach is whereby the needle is inserted into the thyroid cartilage, at the inferior border of thyroid cartilage, approximately 1 cm lateral to midline. The needle advanced in a direction perpendicular to the thyroid cartilage.

Table 2: Equipments required for injection laryngoplasty

<table>
<thead>
<tr>
<th>Equipment/Anaesthesia</th>
<th>Material/Technique</th>
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<tbody>
<tr>
<td>Lidocaine 5%/phenylephrine 0.5% spray</td>
<td>(anaesthesia of nasal cavity)</td>
</tr>
<tr>
<td>Xylocaine 10mg spray</td>
<td>(anaesthesia of oropharyngeal cavity)</td>
</tr>
<tr>
<td>4% lignocaine</td>
<td>(for topical laryngeal anaesthesia)</td>
</tr>
<tr>
<td>2% lignocaine</td>
<td>(anaesthesia of skin)</td>
</tr>
<tr>
<td>Flexible nasal endoscope</td>
<td></td>
</tr>
<tr>
<td>Video monitor connected to flexible nasoendoscope</td>
<td>(Figure 1)</td>
</tr>
<tr>
<td>Injection material eg. Gelfoam, Cymetra, Zyderm, Hylaform, Radiesse Voice gel, Radiesse Voice, autologous fat</td>
<td></td>
</tr>
<tr>
<td>Syringe and injection needle</td>
<td></td>
</tr>
<tr>
<td>Alcohol wipe/Chlorhexidine for skin preparation</td>
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<tr>
<td>Assistant</td>
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Complications

Injection laryngoplasty generally carries fewer risks compared to laryngeal framework surgery. General risks such as bleeding, infection and pain remains applicable. The most significant but rare risk of the procedure is airway obstruction. Airway obstruction can occur secondary to laryngeal spasm, over-medialization of both vocal cords and laryngeal oedema secondary to over-manipulation of the larynx. Ample anaesthesia to the larynx reduces the risks of laryngeal spasm. When bilateral injections are necessary, it should be done with caution in particular with avoiding over-injection.

There is also a risk of allergic reaction towards the injection material. It is important to ascertain the patients' allergic history and that the resuscitation trolley is readily available in the event of emergency. Patients are also at risk of a less than satisfactory outcome. This can be attributed to migration or increased rate of resorption of the injection material. Rarely, it could be due to accidental injection into the wrong site, thereby giving no effect to the patient’s voice. In some instances, the materials can be wrongly injected into the vocal cords, causing oedema and therefore hoarse voice, discomfort or even breathing difficulties. The risk of bleeding from injection is low. In the aforementioned retrospective review by Luu et al, there were 59 patients who were taking warfarin at the time of injection who experienced no bleeding complications.

Conclusion

In conclusion, injection laryngoplasty is a useful procedure as a means of treatment for glottic insufficiency. There are various methods and materials available and thorough understanding is required prior to their use. There is a steep learning curve for this procedure and the senior author’s advice is for the learner to begin in a more controlled theatre environment before advancing to performing the procedure in the clinic setting.

Conflict of Interest

All authors have no conflict of interest to declare. No extraneous funding was obtained.

Transoral injection

Transoral injection can be performed in theatre or clinic setting. Topical anaesthesia is sufficient and skin infiltration is obviated. Xylocaine spray is applied to the nasal, oral and laryngeal cavity. Flexible nasoendoscope is used to visualize the vocal cord and paraglottic area. The patient’s tongue is held with gauze with one hand and the other hand is used to inject. Flexible nasoendoscope is passed by the assistant to visualize the vocal cord and paraglottic area. A distinct 25cm long needle with 16 gauge malleable shaft and 25 gauge needle tip is used to inject the injection material. The needle is bent as appropriate to suit the contour of the pharynx and larynx and then introduced orally. Injection material is injected lateral to the vocal cord where it arises from the vocal process. This will oppose the middle and posterior gap between the vocal cords. Occasionally, a second injection might be required lateral to the mid-vocal fold. It is generally advisable to over-medialise the vocal cords slightly. However, it would be wise to avoid injecting too anteriorly as it will give a strained voice.

Microlaryngoscopic injection

Microlaryngoscopic approach is similar to the transoral approach, with the addition of the necessary general anaesthesia. A 25cm long needle with 25 gauge malleable tip is passed through a rigid laryngoscope under microscopic visualisation. It is generally handy to bend the needle at 90 degrees near its handle, so that the syringe would not obstruct the view of the vocal cords and paraglottic space. Injection site is exactly the same as for transoral approach.
References


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