VILNIUS UNIVERSITY

MEDICAL FACULTY

The Final thesis

Laryngeal Injections for Vocal Fold Palsy

Guy **Brill**, **VI year, 1 group**

Institute of Clinical Medicine, Clinic of Ear Nose and Throat and Eye disease

Supervisor: Lecturer Marius Polianskis

Head of clinic: Prof. Eugnijus Lesinskas

2024

Email of the student: guy.brill@mf.stud.vu.lt

Index:

List of abbreviations:

1. VCP – Vocal Cord Paralysis.
2. RLN – Recurrent Laryngeal Nerve.
3. ITA – Inferior Thyroid Artery.
4. BVCP – Bilateral vocal cord paralysis.
5. UVCP – Unilateral vocal cord paralysis.
6. ECM – Extracellular matrix
7. PCA - Posterior cricoarytenoid
8. TA – Thyroarytenoid
9. SLLP - Superficial layer of the lamina propria
10. HA – Hyaluronic acid.
11. AFIL – Autologous fat injection laryngoplasty.
12. CaHA - Calcium hydroxylapatite
13. EMG – Electromyography.
14. BoNT – Botulinum Toxin.
15. bFGF – Basic Fibroblast Growth Factor.
16. MSC – Mesenchymal Stromal Cells.

1. Summary

Laryngeal injections like hyaluronic acid and autologous fat have made a huge difference in the treatment of vocal fold palsy. Vocal fold palsy can significantly impact the voice and speech, leading to decreased quality of life and increased societal isolation for affected individuals. Vocal fold injection is a procedure known for over 100 years but gained new sympathy with the innovations of new materials and technology, along with new injections methods. (1) Laryngeal injection has been shown to be a safe and effective treatment for laryngeal conditions, with the potential to reduce or even eliminate the use of surgeries. Laryngoplasty injection into the vocal folds was pioneered by Bruening in 1911 and has further evolved ever since. (2) Therapeutic efficacy in these treatments is supported by extensive evidence, known to be the most common and reliable method of laryngeal injection therapy. (3) This work explores the importance of laryngeal injection treatment for various deficiencies in the vocal folds, including the development, mechanism of action uses, and management of laryngeal injection techniques.

2. Key words

Laryngeal injections, the larynx, vocal fold palsy, vocal fold paralysis.

3. Introduction

The vocal folds are mechanically active soft tissues that can produce sound through continuous vibrations in response to air-flow. Voice disorder may lead to decreased occupational performance and impaired quality of life. The number of adults who report having voice disorders at some point in their lives is relatively high and represent as 16.9% of the population in a study by Lyberg-Åhlander at el, and the number of people who work with their voices for a living, like singers and teachers, is increasing. (4) Vocal fold mucosal damage is reported in 60–80% of patients seeking medical help. (5) Damage to the vocal folds can result from numerous factors, including intubation, trauma, chemical irritants, malignancies, inflammations, and laryngopharyngeal reflux. (6) This thesis describes the different injection treatment options for vocal fold palsy and the pathogenesis. In addition, it discusses the different causes and conditions of vocal fold palsy leading to impairment and the treatment with new developments in injection materials and endoscopic assistance as part of the treatment process for vocal fold disorders.

The goal of this thesis is to achieve an understanding of the laryngeal injection treatments for vocal fold palsy. Putting attention to the use of hyaluronic acid and autologous fat as injectable materials, and it actively discusses the treatment procedure, indications, and impact on patient outcomes.

4. Anatomy of the larynx

The larynx's anatomical location changes slightly with age. At infancy and childhood, the larynx is located superiorly compared to its location in adulthood. At puberty, the larynx moves downward, forming the anterior triangle base of the neck. The larynx is connected to the trachea by the cricotracheal ligament and located just above it. The larynx is divided into 3 main parts, the supraglottic, glottis, and subglottic. These parts of the larynx help in the production of voice, protection of the airway, and swallowing. (7) The larynx unique structural combination of cartilaginous, neurovascular and musculature work together to facilitate its complex function. The larynx cartilage is a flexible but also rough structure that can provide support, categorized into unpaired (thyroid and cricoid) and paired (arytenoid, cuneiform, and corniculate). In males, the 2 laminae of the thyroid cartilage join at the laryngeal prominence, forming "Adam's apple". Posteriorly, the two laminae remain open, extending superiorly and inferiorly and forming the superior and inferior horns. The superior horn connects to the hyoid bone with the thyrohyoid membrane and lateral thyrohyoid ligament. The inferior horn connects the cricoid cartilage with the cricothyroid membrane. The thyrohyoid membrane contains a foramen where the superior laryngeal vessels and internal branch nerve pass. The cricoid cartilage is unique for its shape of ring, is composed of hyaline cartilage and provides structural support. The arytenoid cartilage is bound to the vocal ligament and to the intrinsic laryngeal muscles. Together, the arytenoid and cricoid cartilages connect through the ball and socket joint, forming adduction and abduction movements for voice production and protection. (8)

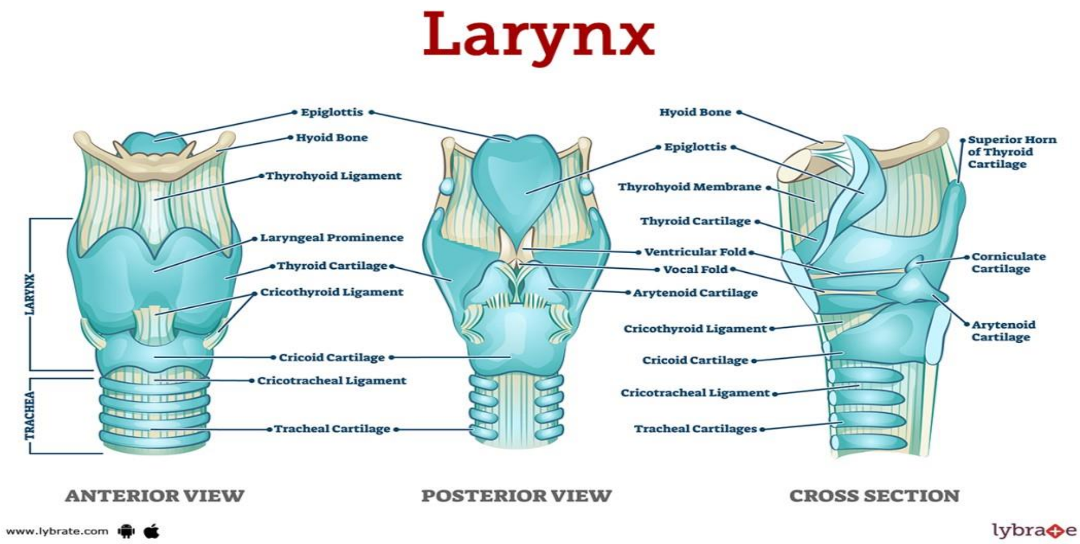

Figure 1- the larynx (9)

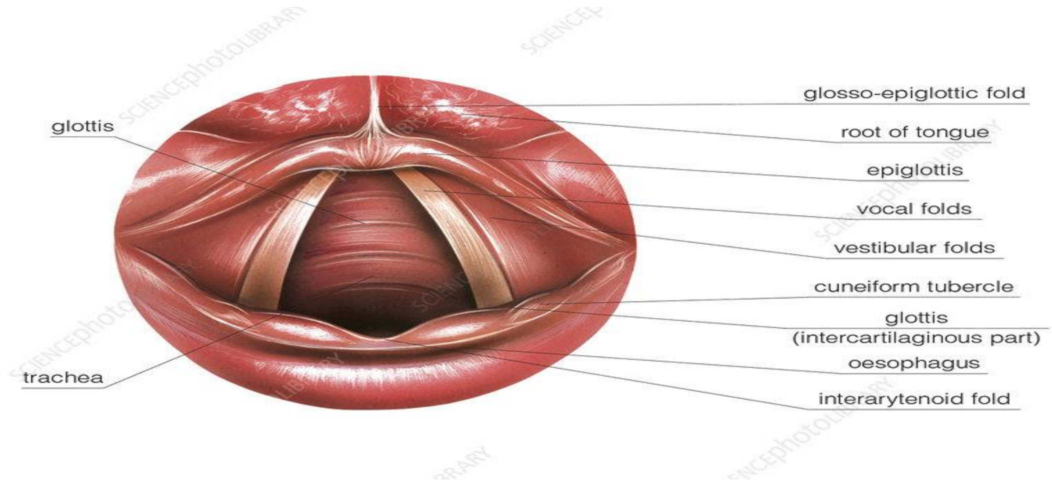

Figure 2- the vocal cords (11)

4.1. Musculature

Divided into external and internal musculature. The primary function of the external muscle is swallowing, and they separated into subgroups:

- The infrahyoid muscles include the sternohyoid, sternothyroid, and omohyoid muscles. Responsible for depression movement of the larynx and receiving innervation from the C1-C3 nerve roots.
- The suprahyoid muscles include the geniohyoid, digastric, thyrohyoid, mylohyoid, and stylohyoid muscles. Responsible for elevating the larynx and receiving innervation from C1, CN V3, and CN VII.
- The superior, middle, and inferior constrictors muscles are innervated by the pharyngeal plexus. Their main function is to move food while wallowing.

The internal muscle's main function is to produce sound and assist breathing by abducting or adducting the vocal folds. Classified into adductors and abductors:

- The posterior cricoarytenoid muscle, which is the abductor muscle of the vocal folds, receives innervation from the external branch of the superior laryngeal nerve.
- The lateral cricoarytenoid, thyroarytenoid, intrearytenoid, and cricothyroid muscles are the adductor muscles of the vocal folds. They receive innervation from the recurrent laryngeal nerve. (12)

The pars recta and pars oblique, known as the two bundles of the cricothyroid muscle, tense the vocal folds to achieve a high voice. Pars recta, which is oriented vertically, induces an anterior rotation of the vocal folds around the cricothyroid joint when in contraction. Then the pars oblique shifts its attachment to the back of the cricothyroid cartilage. The combined actions of the pas recta and pars oblique increase the tension and length of the vocal folds, resulting in a higher voice. (7)

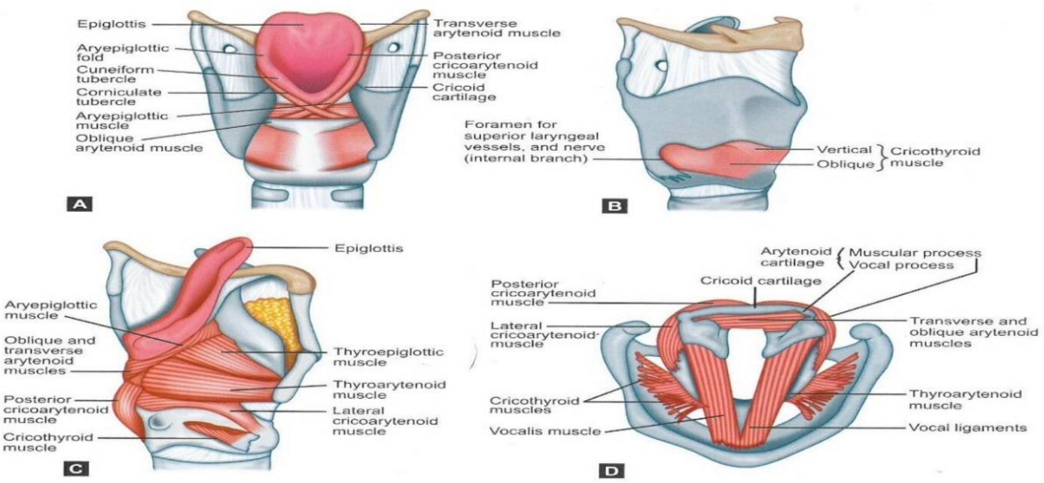

Figure 3- The intrinsic muscles of the larynx (13)

4.2.Vasculature

The blood supply of the larynx is mediated mainly by two major arteries: the external carotid artery and the subclavian artery. The external carotid artery branches into the superior thyroid artery, below the level of the superior cornu in the hyoid bone, which further branches into the infrahyoid artery, superior laryngeal artery, cricothyroid artery, and the sternocleidomastoid artery. These arteries supply their corresponding muscles, while the cricothyroid artery supplies the isthmus and pyramidal lobe of the thyroid.

The inferior thyroid artery (ITA) is a branch of the thyrocervical trunk that originates from the subclavian artery. The ITA goes posteriorly and medially to the carotid and branches off into the pharyngeal arteries, which are the main blood supply of the larynx. In addition, the ITA supplies the four parathyroid glands. The ascending cervical artery supplies the neck and small spinal arteries. The inferior laryngeal artery has anastomosis with the superior laryngeal artery and courses along with the recurrent laryngeal nerve. Both supply the larynx.

The superior and middle thyroid veins drain into the internal jugular vein. The inferior thyroid vein drains into the subclavian vein and further into the brachiocephalic veins, which form the superior vena cava. The deep cervical, paratracheal, pre-tracheal, and pre-laryngeal lymph nodes are the lymph drainage pathways of the larynx. In addition, the recurrent laryngeal lymph node is the most common site for metastasis in esophageal squamous cell carcinoma. (14)

4.3.Nerves

The primary innervation of the vocal folds is provided by the branches of the vagus nerve, the superior and the recurrent laryngeal nerve. (15) The superior laryngeal nerve divides into the external laryngeal nerve and the internal laryngeal nerve proximal to the greater horn of the hyoid bone. They give sensory innervation to the mucosa above the glottis, providing general and taste sensation from the epiglottis. The internal laryngeal nerve can be approached for anesthesia induction beneath the medial wall of the piriform fossa. The external laryngeal nerve gives motor innervation to the cricothyroid muscle. It is located proximal to the superior thyroid artery and proximal to the upper part of the thyroid gland. (8)

The recurrent laryngeal nerve (RLN), also known as the inferior laryngeal nerve, gives motor and sensory innervation below the level of the vocal cords. The RLN has an indirect course under the arch of the aorta on the left and loop around the subclavian artery on the right. Eventually, it moves posteriorly to the cricothyroid joint and enters the larynx through the inferior constrictor muscles. The RLN has various anatomical variations that could increase the risk for iatrogenic damage during surgical procedures. The most common variation is the extra-laryngeal branches, usually located at the ligament of Berry, and often present as a thyroid with large goiter.(12)

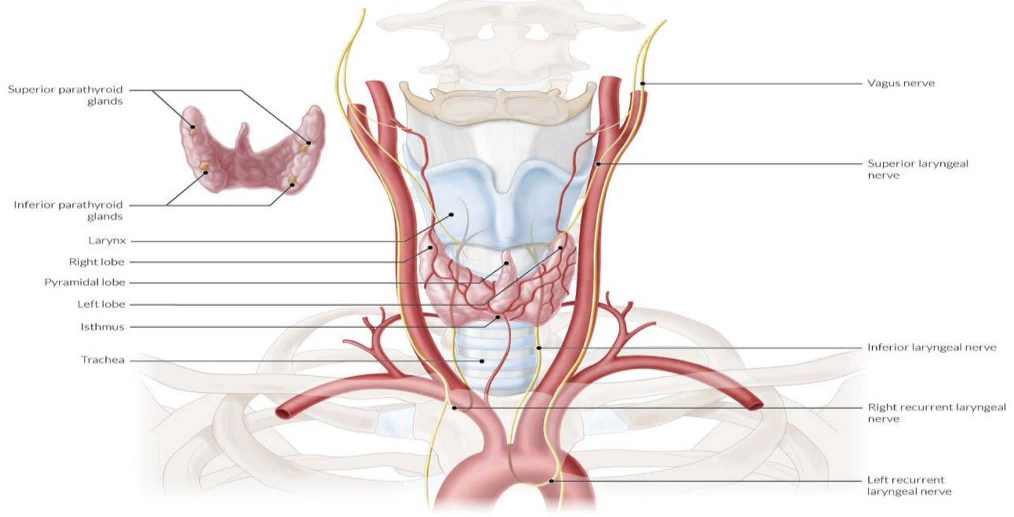

Figure 4 - Thyroid gland and relations to surrounding structures.(16)

5. The vocal folds

The vocal folds are part of the vocal system, including the lungs and the lower airway. The vocal folds modulate airflow to produce voice through vibration. Located in the larynx, each vocal fold is about 11–15 mm long in women and 17–21 mm in men. They stretch across the larynx anteriorly and posteriorly, anteriorly attached to the thyroid cartilage and posteriorly to the arytenoid cartilage. The vocal folds are composed of a deep muscular layer, a soft tissue layer of the lamina propria, and an outermost squamous epithelium layer. (17) The lamina propria layers can be divided into superficial, intermediate, and deep layers. The superficial layer of the lamina propria (SLLP) is important for vibration and voice prosuction. (10) The intermediate layers form the vocal ligament, while the superficial layers provide the gelatinous surface. Trauma from surgery can particularly injure these 2 layers. (18) The extracellular matrix (ECM) composition primarily impacts the viscoelasticity of the vocal folds. (19) The two primary ECM proteins in the vocal folds are collagen and elastin. (17) Collagen type III is most common in the lamina propria, while elastin is most abundant in the intermediate layer, and neither constitutes a significant part of the superficial layer. Elastin gives the vocal folds tissue its elastic properties and is found primarily in the superficial layer. Collagen function is to provide mechanical support for high-frequency vibration and stretching. (20)

In addition, the vocal folds can be highly prone to inflammation due to sensitivity to airborne particles, which can upregulate inflammatory molecules like interleukin-6 (IL-6) and IL-1β, leading to an inflammatory response via mitogen-activated protein kinase (MAPK) and necrosis factor kappa beta (NF-κB) pathways. (19)

6. Vocal fold palsy

Vocal fold palsy is a condition in which quality of life is impaired in voice production, breathing and swallowing. It refers to obstruction in the mobility of the vocal folds due to the pathology of the vocal fold itself or of the motor nerve that innervates the muscles responsible for vocal folds movement. (21) Vocal fold palay divides into vocal fold paralysis (VFP), which describes true immobility, and vocal fold paresis, characterized by weakening mobility of the vocal cords. (22) Unilateral vocal fold palsy is far more common than bilateral palsy and is a relatively common presentation in outpatient clinics. The vocal cords serve two functions, production of voice (phonation) and protection of the lower airways through glottic competence. If the location of the paralysis is more medially, stridor and breathing symptoms can be more pronounced, while lateral paralysis may lead to significant voice disorder due to the patency of the airway route and the inability to close it. Clinically, the symptoms include hoarseness, vocal fatigue, loss of vocal pitch, dysphagia, shortness of breath and possible life-threatening aspiration. (6) The impact on quality of life is often significant, especially for patients who rely on their voice for a living, like teachers or singers. (21) The damaged vocal cord or arytenoid joint is characterized by the replacement of normally mobile tissues with fibrosis and scar tissue, resulting in mechanical tethering and preventing normal movement. (23) During this process, type III collagen is replaced with type I collagen, ECM proteins decrease, and viscoelastic properties change as hyaluronic acid production is reduced. All of which leads to impaired vocal fold movement. (19) The muscles responsible for vocal cord movement are primarily innervated by the RLN, branches of the vagal nerves, and the external branch of the superior laryngeal nerve. The underlying pathogenesis involves a lesion or other disruption along the course of the vagal nerves above the branching of the RLN, the external branch of the superior laryngeal nerve, or directly on the recurrent laryngeal nerve, which is more common. Other conditions that can cause VFP include surgery, malignancy, trauma, infection, systemic diseases, and inflammation. Iatrogenic injury due to mediastinal and neck surgery is the most common cause. (6) As the primary cause is post-surgical nerve injury, it is mainly seen in the age group of 50-60 years, probably because of the history of chronic smoking and the higher incidence and prevalence of cancer and systemic co-morbidities like diabetes and hypertension. (24) For diagnosis, several investigation tools can be utilized, including flexible fiberoptic examination, direct laryngoscopy, laryngeal electromyography, CT or MRI scan, and If the diagnosis is still uncertain, a video stroboscope and bronchoscopy can be used. (23) The management depends on the underlying etiology, anatomy, and prognosis. Voice therapy is the initial step, regardless of the underlying etiology, given that up to 60% of cases resolve spontaneously. (25) For inflammatory and infectious conditions, specific treatments like corticosteroids or antibiotics are effective. Glucose and anti-reflux therapy are indicated for diabetes-related neuropathy and recovering patients with reflux, respectively. The management of bilateral vocal fold paralysis is typically more aggressive than unilateral vocal fold paralysis, with surgeries being the most common method of treatment for bilateral paralysis. Unilateral vocal fold paralysis has a better prognosis, therefore, the management is more often injection laryngoplasty as the first line treatment. For patients with poorer prognosis, a more invasive approach is indicated, including laryngeal framework surgery, RLN re-innervation, or laryngeal pacing. (26) The prognosis is most dependent on the etiology, while spontaneous recovery is expected in 55% of patients, a full recovery can be very prolonged. (23) Recovery can be complete or incomplete, highlighting the complexity of this condition, which requires an individual approach for each patient. (27)

6.1. Vocal fold palsy Etiology

Vocal cord paresis is often the initial finding of a disease that may develop into vocal cord paralysis, it might as well not progress and remain as paresis. Progress depends on the underlying etiology. Several factors can result in scarring of the vocal cords, including radiation therapy, prolonged intubation, and inflammatory diseases. (28) (23) These may lead to impairment of vocal cord motion and can progress to glottic stenosis. (6) Wallerian degeneration, a peripheral nerve response to traumatic nerve injury, can further worsen injured nerves, often due to surgical trauma, resulting in a scar replacement of the destroyed nerve end. (29) Malignancy of the glottis, especially the supraglottic, should be suspected when symptoms such as unilateral throat pain, referred otalgia, dysphagia, unexplained weight loss, or neck mass are presented. (25) Central nervous system injuries affecting the vagal nerve nuclei (the nucleus ambiguous and nucleus solitarius) can also contribute to impairment in vocal cord motion. As can systematic diseases such as amyotrophic lateral sclerosis and Guillain-Barre syndrome impacting nerve function. (6) Diabetes mellitus, a condition associated with peripheral neuropathy, can increase the risk of developing vocal fold palsy. (24) Other possible causes that are more related to unilateral vocal cord paralysis are neurological disorders like stroke or infectious diseases such as varicella zoster or Lyme disease. RLN Injuries following trauma or arytenoid dislocation may lead to unilateral vocal fold paralysis as well. (24) Damage to the RLN affects both abduction and adduction of the vocal folds. Since the adductor muscle is significantly bigger than the abductor muscle, after an injury, the vocal cords assume a static paramedian position. (23) Notably, the left RLN is more prone to injury due to its longer course. The conditions that often have a poor prognosis for recovery are advanced laryngeal malignancies, systemic diseases such as Miller-Fisher syndrome, and central nervous system injuries. (30) In pediatric cases, common etiologies are neurological, traumatic (including birth trauma), and iatrogenic (post-surgery complications). In addition, congenital conditions such as Arnold-Chiari malformation II with hydronephrosis have been associated with bilateral vocal fold paralysis. (23) Among secondary malignancy-related-causes, lung cancer, which most commonly affects the left vocal cord, thyroid malignancy and esophageal cancer cause vocal fold palsy due to nerve invasion and compression. Iatrogenic injuries from thyroid, esophagus and heart surgeries due to injury to the RLN or superior laryngeal nerve are the most common etiology. Usually unilateral, but can be bilateral rarely in cases of total thyroidectomy. (24) Endotracheal intubation is also responsible for many RLN injuries, causing vocal fold palsy, with arytenoid dislocation as a possible cause. (27) Additional factors that are more related to glottic insufficiency but also contribute to VFP are age-related central bowing of the vocal folds, conditions such as sulcus vocalis, and vocal fold nodules. (25)

6.2. Diagnosis of vocal fold palsy

To diagnose the functionality of the vocal fold, several investigation tools can be utilized. Flexible fiberoptic is the initial physical examination that asses vocal cord movement, it can rule out laryngomalacia, which can have similar presenting symptoms. Direct laryngoscopy and bronchoscopy under anesthesia may be required if there is uncertainty regarding the condition of the vocal cords or a lower airway issue, and they allow examination of the arytenoid joints to rule out fixation or alternate pathologies such as subglottic stenosis and bronchomalacia. (23) Laryngeal electromyography (EMG) determines the innervation status of the laryngeal muscles, can clarify the duration of the paralysis and predict the prognosis of recovery, and uses a percutaneous EMG needle to perform an electrophysiological evaluation of the intrinsic muscles of the larynx. (31) A CT scan is the preferred imagining choice for the RLN and helps identify signs of paralysis or a mass lesion. MRI is another possible option, especially if the diagnosis is still uncertain. (32) A video stroboscope can provide additional information about the vocal cord vibrations and rule out subglottic and tracheal pathology. (23) In addition, neck and laryngeal ultrasound can help in the assessment of the vocal cord movement and surrounding pathologies, although it is a less common method.

7. Bilateral vocal fold paralysis

Bilateral vocal fold paralysis is also known as bilateral vocal cord paralysis (BVCP). Primarily caused by injury to the vagal nerve, either from its cerebral origins or from the branches that reach the thorax and abdomen. Due to some redundancy, the location of the vocal cords is not always a reliable predictor for the site of the lesion. (23) Injury to the RLN is the most common cause. Typically, decreases the pitch of the voice and can lead to a bowing deformity of the vocal cords due to a loss of tensile tone from the paralyzed cricothyroid muscle. A significant vagal injury can lead to a nearly fully abducted ("cadaveric") vocal cord position. (27) The primary presentation of a patient with BVCP is voice changes, including hoarseness and voice fatigue. These patients can also experience breathing difficulties such as stridor, increased work of breathing and aspiration pneumonia. In children, BVCP often presents with stridor, feeding difficulties and more severe manifestations such as cyanosis and apnea, particularly in congenital cases. However, because the vocal cords remain in the paramedian position in pediatric patients, their condition typically has no effect on voice quality. Contrary to adults, children usually present with a normal voice because the vocal cords remain in the paramedian position. In infants and children primarily presenting with stridor, congenital bilateral vocal cord paralysis is the most common cause. In infants, cardiovascular surgery is another common cause of BVCP. (23)

Surgery is the main treatment, including permanent intervention such as a cordotomy or arytenoidectomy for conditions involving airway obstruction and irreversible damage to the vocal folds. A reversible procedure like a tracheostomy or botulinum toxin injection may be indicated for cases with a better prognosis.(23)

8. Unilateral vocal fold paralysis

Unilateral vocal cord paralysis is also known as unilateral vocal cord paralysis (UVCP). A common presentation with symptoms including dysphonia, shortness of breath and swallowing difficulties. It occurs due to damage to the RLN by various causes, such as cancer, trauma, or surgery. Iatrogenic surgical injury is the most common type of injury, typically after thyroidectomy or parathyroidectomy operations. Although intra-operative nerve stimulators are frequently used to avoid injury, their effectiveness has not been clinically proven. Malignancy is the most concerning cause, which is most seen in primary or metastatic lung cancer and laryngeal carcinoma. Other less common causes of UVCP include neurological conditions (stroke, myasthenia gravis, multiple sclerosis), inflammatory diseases (sarcoidosis, systemic lupus erythematosus), and infectious diseases (Varicella zoster, Lyme disease). Idiopathic paralysis is poorly understood and should only be diagnosed when all other causes have been excluded, it is thought to be secondary to a viral or inflammatory disease. Patients typically present with a sudden onset of dysphonia, often described as a weak or "breathy" voice. In addition to voice change, many patients may present with swallowing difficulties such as dysphagia and regurgitation. Additionally, patients can experience shortness of breath despite normal lung function.

The initial treatment choice for UVCP is voice therapy and rehabilitation with speech and language therapists. It can be used both before and after surgical intervention. The goal of this therapy is to improve glottic closure by increasing intra-abdominal pressure through techniques like humming and abdominal breathing. Early use of voice therapy may help avoid or delay the need for surgery. (21) For patients with poor prognosis, more invasive treatment options may be applicable, including laryngeal framework surgery, RLN re-innervation, and laryngeal thyroplasty. These approaches used to be the main treatment after conservative management, but now the current approach is to start with laryngeal injection of various fillers including hyaluronic acid and autologous fat tissue. The aim of surgical management is "medialization" of the affected vocal cord to improve voice quality. Traditionally, the treatment approach is to wait 6 to 9 months between check-ups visits to allow spontaneous motion before proceeding with surgical treatment. (26) Type 1 Isshiki thyroplasty is a permanent medialization procedure for the treatment of vocal fold paralysis to improve voice and swallowing outcomes. (33) The technique involves cutting a window into the thyroid cartilage and moving the vocal cords medially with the use of an implant. Although there are complications related to this procedure, such as airway compromise or hematoma, most patients do well, and voice outcomes are reported to be successful at 1 and 3 years after the operation. (21) Laryngeal reinnervation aims to establish vocal cord abduction by utilizing functioning nerves and restoring the activity of the posterior cricoarytenoid (PCA) muscle, it does not affect adduction. (23) In general, there is no one technique that has shown statistically better results in terms of voice outcomes or quality of life compared to others. (21)

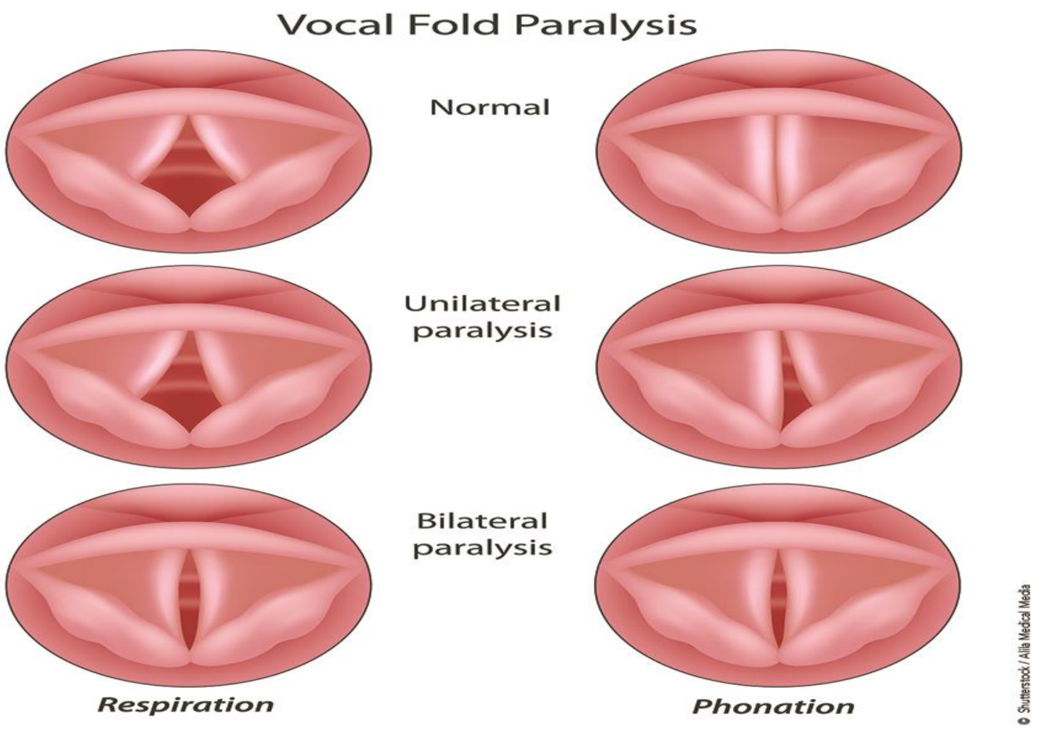

Figure 5 – Vocal fold paralysis.(34)

9. Laryngeal injections for vocal fold palsy

Laryngoplasty injection was first described by Bruening in 1911 and has evolved since in terms of techniques and materials. In recent years, it has gained popularity due to its low cost, ability to avoid general anesthesia, technical simplicity, and good efficacy. (35) Laryngeal injections involve the administration of a substance proximal to the injured vocal fold to restore its bulk and form, with the goal of moving it medially and improving contact with the opposing cord to increase vocal function. (22) It can be performed under general anesthesia or with local anesthesia. (36) Procedures with local anesthesia allow for real-time patient feedback in terms of the improvement of voice outcomes. It provides the ability to make fast adjustments. This approach also avoids possible complications of general anesthesia and suspension laryngoscopy, including dental damage, tongue numbness, and taste disturbance. However, patients with neuromotor disorders, excessive gag reflex, and oropharyngeal dysphagia are recommended to undergo the procedure in an operating room under general anesthesia to ensure safety and effectiveness. (22) The complications associated with laryngeal injections are bleeding, infection, pain, and airway obstruction. Airway obstruction is the most significant but rare complication and can be caused due to laryngeal spasm, over medialization of the vocal folds, or laryngeal edema from overmanipulating the larynx. Administration of adequate anesthesia to the larynx reduces the risk of spasm. (35) There are no absolute contraindications to laryngeal injection except if the patient refuses treatment, has an allergy to the injectable substances or there is a condition of irreversible obstruction of the airway, such as severe damage to the recurrent laryngeal nerve. The injectable material may be classified into short and long-term. Short-term materials most commonly include bovine and porcine gelatin, carboxymethylcellulose, hyaluronic acid, and collagen-based products. Long-term materials, lasting for a minimum of 1 year, include autologous fat and calcium hydroxyapatite. (22) Teflon used to be an option, but it’s less common due to complications such as granuloma formation. Despite the variety of options, none is proven to be better than another in terms of efficacy and safety. (27)

Vocal fold injection has several limitations. A glottic gap of up to 3 mm is generally considered suitable, larger gaps are typically difficult to correct. In cases of posterior glottic gaps or significantly foreshortened vocal folds, arytenoid adduction is usually performed in conjunction with laryngeal injection to provides better results. (1)

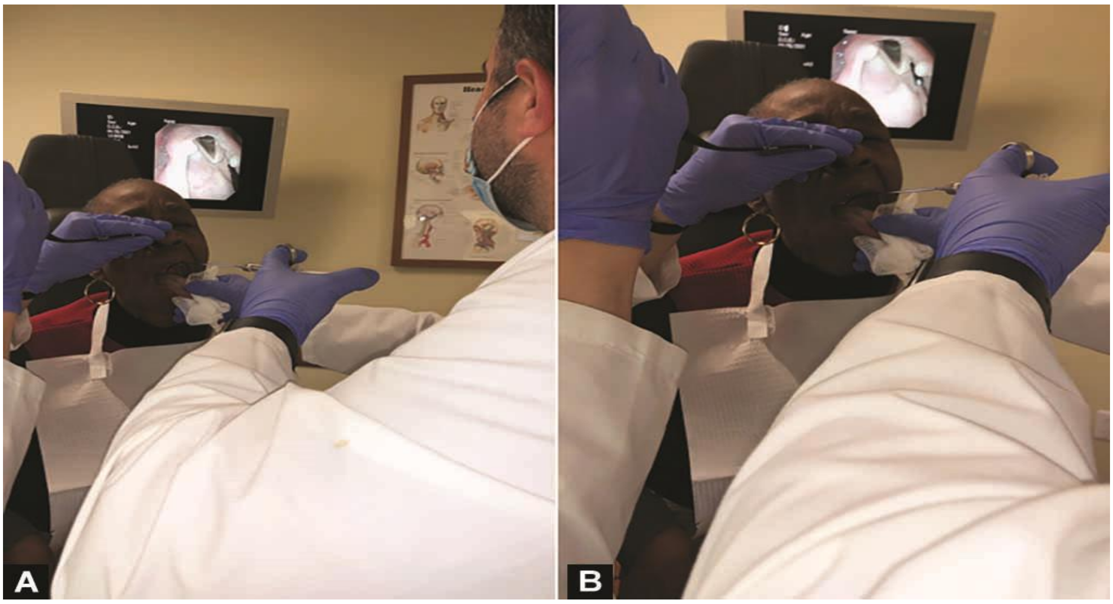

Figure 6 – Laryngeal injection.(22)

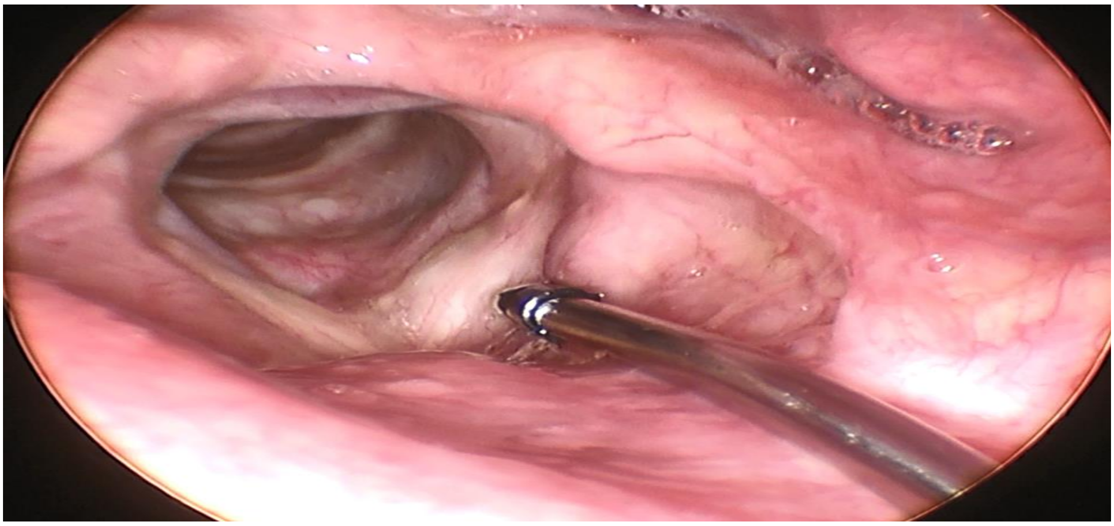

Figure 7 - Injection to anterior left vocal cord.(37)

9.1. Hyaluronic acid laryngeal injection

Hyaluronic acid (HA) is a high-molecular-weight, natural polysaccharide that is part of the ECM found in all tissues, especially mechanically active tissues like vocal folds, cartilage, and dermis. (38) The molecule is synthesized in the inner plasma membrane by a transmembrane protein family called hyaluronan synthases and moved out into the ECM, where it is degraded by the enzyme hyaluronidases. (10) It is highly concentrated in the lamina propria of the vocal folds, where the bioactive glycosaminoglycan properties maintain the optimal viscoelastic properties of the vocal folds. HA consists of repeating units of D-glucuronic acid and N-acetyl D-glucosamine, the preparation is made of cross-linked chains, which form a linear polysaccharide chain, viscous gel. (38) HA interacts with water to form extensive hydrogen bonds, allowing it to undergo deformation and resist trauma by expanding up to 1000 times in weight, acting as a space filler, shock absorber, and tissue damper that can absorb the continuous stress from the constant vibration applying to the vocal folds without causing permanent damage. At a physiological pH, the negatively charged polarized HA interreacts with ions, regulating tissue viscosity, osmosis, and hydration, thereby regulating vocal quality. (10) In addition, HA promotes the recruitment of fibroblasts, which yield new connective tissue and lead to endogenous soft tissue augmentation that can support and repair the vocal folds. (39) The effect typically lasts 3 to 9 months before reabsorption, with some voice improvement seen up to 12 months. (22) While considered safe to use due to low tissue reactivity, it has been associated with several adverse effects, including minor ones like erythema, edema, and irritation, as well as more serious complications such as foreign body granuloma formation, necrosis, allergic reactions, dyspnea and dysphonia.(19) Despite these potential complications, the HA profile as a viscoelastic material similar to human vocal folds makes it an ideal option for injection laryngoplasty for the treatment of UVCP**.** (35)

9.2. Sodium carboxymethylcellulose laryngeal injection

Sodium carboxymethylcellulose is combined with glycerin and water to form a gel (known as voice gel). (35) Voice gel is commonly used for vocal fold augmentation procedures including reversible vocal fold paralysis and other forms of glottic incompetence. (1) It can last up to 1–3 months, there is no need for preparation or harvesting the injection material, and no prior allergic testing is required. In addition, because sodium carboxymethylcellulose has no infection transmission risk, the complication risk is very low, making it a very safe choice of material. (40)

9.3. Collagen-derived material laryngeal injection

Collagen is a fibrous protein in the extracellular matrix that has viscoelastic properties, which contribute to voice production. Although, it does not directly affect the stretching of the tissue, it provides structural support, establishes the elasticity threshold during stretching, and ensures tissue integrity. Collagen similarity to host tissue in the lamina propria makes it an appropriate choice for vocal fold filler. It supports the growth of host tissue, can be replaced by host collagen, and heals scar tissue. Injections of collagen preparation have been used to augment vocal folds and improve function. These have included soluble bovine collagen products, and cross-linked bovine preparations. Complications associated with the use of bovine collagen include autoimmune responses, airway complications, and immune reactions that lead to the destruction of the material. Therefore, human-derived forms of collagen preparation like autologous, homologous, and micronized AlloDerm have been developed for use in laryngoplasty injection. Autologous collagen preparations can resist degradation, however, the amount required is a limited factor because the donor material originates from the patient's skin. Homologous collagen injection into the SLLP and the medial part of the thyroarytenoid (TA) muscle led to improved muscle contraction and vocal fold vibratory pattern. However, injection only into the SLLP does not appear to improve the voice outcome. (20) Micronized AlloDerms, an acellular dermal matrix composed of collagen, elastin, and laminin, are an efficient preparation for the treatment of vocal fold paralysis, sulcus, scars, and presbyphonia. (41) Additionally, hydrogels of collagen have been used in tissue engineering and augmentation for their ability to facilitate cell attachment and migration. Hydrogels can modulate cell function by mimicking the microenvironment, and they are less at risk of immune rejection because of their structural similarity to the physiological ECM. (20) Bovine-based collagen can last approximately 2 to 4 months and carries a low risk of allergic reactions. As a result, the FDA recommends allergy testing prior to use. Human-derived collagen has variable durability from a few months to over a year, and while there is a potential risk of infection transmission, there have been no cases reported, and it is generally considered safe to use. (22)

9.4. Autologous fat laryngeal injection

Autologous fat injection laryngoplasty (AFIL) was first presented in 1998 as a treatment for UVFP. (26) It is an autologous procedure, utilizing the patient's own fat tissue, and consider as a safe treatment, with minimal potential risk of allergic reaction. (35) AFIL aims to provide a permanent effect due to the adipose stem cells found in the autologous fat, these cells can also increase the formation of new fat cells and are believed to enhance the effect of the treatment on the larynx. It is a long term material lasting for more than a year, with some studies showing efficacy of 26 months and more. (35) Several factors affect the quality of the harvested fat, including the harvesting technology employed, characteristic differences between an individual's fat tissue, and the tissue reaction of autologous fat to the surrounding laryngeal tissues. (26) The fat tissue is biocompatible, nontoxic, easy to obtain, and inexpensive. In addition, its viscosity is similar to that of the lamina propria of the vocal fold. (42) The harvesting is commonly obtained from the subcutaneous tissue of the lower abdominal wall, although other places, like the area superficial to the left trochanter, have also been used. (36) Proper harvesting techniques are crucial for the survival and effect of AFIL, as prolonged exposure to air and high centrifugation speed can damage the adipose stem cell. The harvested fat can remain separated for up to 10 minutes, with the superficial layer removed before injection. Processing methods for harvesting vary, there are studies employing centrifugation, while others combine manual selection and agitation in a syringe or separate fat from connective tissue manually. (42) To increase the survival rate of the harvested fat, combinations such as the addition of insulin because of the stimulation of insulin growth factor (IGF-I) in the fat cell or the addition of platelet-rich plasma (PRP) can be used. This attempt to reduce the rate of reabsorption is the main disadvantage of AFIL. Studies have reported a 50% reabsorption rate 4 years following treatment therefore, the common practice is to use multiple injections. (26) AFIL can be performed transcutaneously through the neck or transorally, the procedure requires general anesthesia, and there are reports of temporary post-operative dysphonia up to 3 weeks. (43) AFIL is considered as a safe procedure with good efficacy for treating UVFP. However, to optimize the longevity and efficacy of the treatment, proper handling of the fat graft harvesting, processing, and injection is necessary. (26)

9.5. Autologous fascia laryngeal injection

Autologous fascia was introduced in 1998 for the use of laryngeal injection, with the advantages of low metabolic requirements, more stability, and less risk of resorption compared to autologous fat or collagen. Fascia can be harvested from the fascia lata, temporal fascia, rectus abdominis sheath, or aponeurosis of the anterior abdominal wall. Fascia lata is the preferred donor site due to the large amount of tissue and accessibility. (35) It has a minimal risk of allergic reactions, infection transmissions or foreign body adverse reactions. (44) In addition, there is no record of scarring or fibrosis following injection. Studies have shown a significant improvement in voice quality after treatment. (35) Autologous fascia provides a long-term effect as an augmentation treatment for the vocal folds, some studies indicate it can range from 3 to 10 years, while other resources state that it can last up to 1 year. (36) However, it is more suited for patients with a smaller glottic gap, and there is a potential risk of donor site morbidities. (35) Furthermore, fascia has been used as an injection therapy in other vocal fold conditions, such as sulcus vocalis, and the short-term resorption rate reduces the need for multiple injections compared to other materials like autologous fat or calcium hydroxylapatite. This treatment option is not widely used, though, since the method for processing harvested fascia is not well known. (44)

9.6. Calcium hydroxylapatite laryngeal injection

Calcium hydroxylapatite (CaHA) is a natural mineral found in human bones and teeth and is an FDA-approved substance for laryngeal injection treatment. The injectable form contains microspheres of CaHA suspended in a carboxymethylcellulose carrier gel consisting primarily of water and glycerin. The gel is reabsorbed and eventually replaced with soft tissue proliferation. (45) CaHA injection provided adequate medialization of the vocal folds up to 12 months, without migration or resorption. It produces excellent results of moderate improvement at 12-month follow-up, and some clinical trials show that persistent medialization may be present for up to 2 years and more, with an average duration of 18 months. (1) Although CaHA is a naturally occurring mineral in the human body and should therefore be biocompatible, there have been rare reports of giant-cell foreign body reactions to CaHA. Additionally, the impact on the viscous-elasticity of the vocal fold is unknown. (35) In general, CaHA have been shown to be highly biocompatible, with little inflammatory response, and studies have proven it is safe to use. (45)

10. Laryngoplasty injections technique

There are 3 approaches to injection laryngoplasty: transcutaneous, transoral and microlaryngoscopic injection. A transcutaneous approach can be performed by placing a needle through the cricothyroid, through the thyrohyoid, or through the trans-cartilaginous. (36) The patient can be positioned sitting upright in a chair or lying flat with the neck slightly extended to allow access to the neck and larynx. (35) Prior to performing the procedure, the hyoid bone, thyroid cartilage, and cricoid cartilage are marked in the midline. The nasal cavity, larynx, and skin are anesthetized, After the skin is numb, the endoscope is passed trans-nasally and suspended above the larynx by an assistant to visualize the vocal cord and paraglottic area. The injectate needle is directed toward the posterior vocal fold. For conditions of vocal folds with reduced mobility, the injection is directed lateral to the vocal process. The goal of this injection is to rotate the arytenoid medially and medialize the true vocal fold. A second injection, if necessary, is placed more anteriorly at the midportion of the vocal fold. (36)

10.1. Cricothyroid approach

This approach involves the insertion of the needle through the cricothyroid membrane, which is located between the thyroid and cricoid cartilage, inferior to the vocal folds. The needle is inserted at the cricothyroid notch in the midline neck and directed superior-laterally into the para-glottic space, which is visualized with an endoscope passing the airway. At this point, the injection material is administered until a desired position of the vocal fold is achieved. (36) In obese patients and in patients with previous neck surgeries, finding anatomical landmarks is usually difficult and challenging. In addition, the oblique direction of injection can make it difficult to assess needle depth and placement. (35)

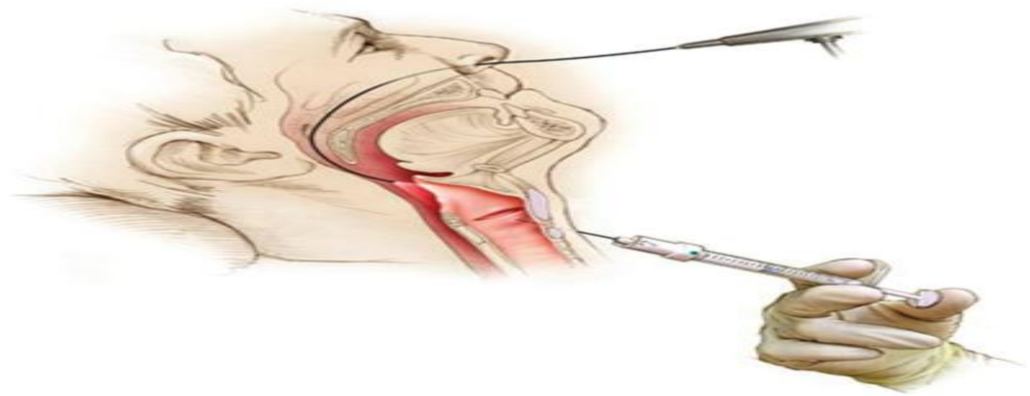

Figure 8 – Cricothyroid approach for percutaneous injection.(46)

10.2. Thyrohyoid approach

In this approach, the needle is inserted at the thyroid notch, through the thyrohyoid membrane, in an inferior direction towards the paraglottic space. The thyrohyoid membrane connects the superior hyoid bone to the inferior thyroid cartilage. When the needle enters the airway, it can be visualized with the endoscope and is directed laterally into the paraglottic space, where the injection is given. (36) The advantage of this approach is the ability to place the needle under direct visual inspection. However, it has the disadvantage of leakage from the needle puncture. (35)

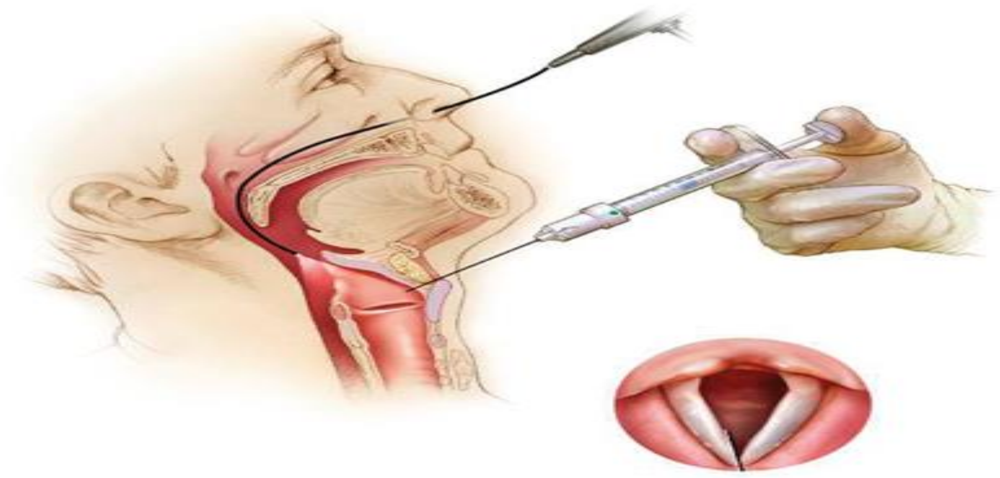

Figure 9 - Thyrohyoid approach for percutaneous injection.(46)

10.3. Trans-cartilaginous approach

The trans-cartilaginous approach involves addressing the vocal folds laterally. (36) The needle is inserted through the thyroid cartilage, 1 cm lateral from the midline, at the inferior border. The needle is directed perpendicular to the thyroid cartilage into the paraglottic space. For additional injection, the position of the needle tip should be located subcutaneously with gentle movements by the surgeon. This method is better for patients who have had prior neck surgeries, where identification of the cricothyroid notch can be difficult. (35) In general, it is recommended to use this approach in younger patients because of the lower risk of thyroid cartilage calcification. (22)

10.4. Transoral injection

The transoral approach is used for patients with thick necks or when neck injections are contraindicated. For this approach, the patient needs to extrude their tongue while the practitioner holds and stabilizes it using gauze. The patient is requested to keep the mouth open without vocalizing. (22) An endoscope is used to visualize the vocal cord and paraglottic space. A distinct 25-cm-long needle is used for the injection material. The needle can be bent to fit the structure of the pharynx and larynx and then inserted orally. Once the needle is visualized above the glottis, the tip of the needle is advanced into the paraglottic space. Injection material is injected lateral to the vocal cord, which will counteract the middle and posterior gaps between the vocal cords. (35) For further medialization, a second injection can be administered lateral to the vocal fold. However, it is recommended to avoid injecting too anteriorly, as it will cause the patient to have a strained voice. In addition, reaching Reinke's space (a subepithelial space within the true vocal fold) during the injection should be avoided due to possible complication such as stiffening of the vocal fold and dysphonia. (22,47) The microlaryngoscopic approach is similar to the transoral approach, with the addition of using general anesthesia. The needle tip is passed through a laryngoscope under microscopic visualization, and the injection site is the same as for the transoral approach.(35)

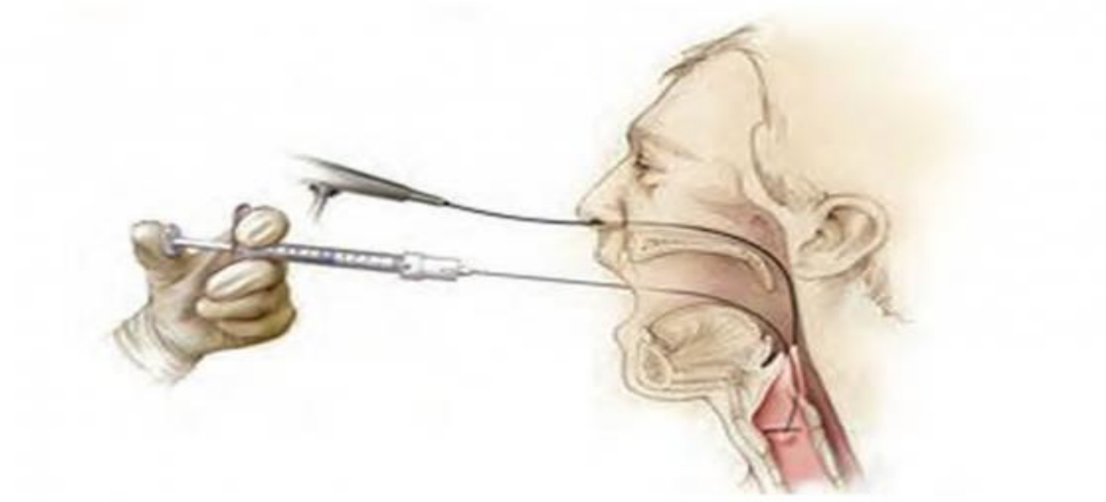

Figure 10 – Transoral injection approach.(48)

11. Other laryngeal injection materials

There are several other materials used for laryngeal injection, including botulinum toxin (BoNT), steroids, growth factors, mesenchymal stromal cells (MSC), gene therapy, and others, to treat various laryngeal conditions.

11.1. Botulinum toxin laryngeal injection

BoNT injections can be an effective treatment option for milder conditions of BVCP with a good prognosis for recovery. In addition, it is the first-line treatment for various laryngeal conditions such as spasmodic dysphonia, voice tremor and muscle tension dysphonia. BoNT, made by the bacterium Clostridium botulinum, inhibits acetylcholine secretion at the neural ends of the neuromuscular junction. (49) It can prevent incorrect contraction of the adductor muscles, leading to improvement of these muscles' function and improving passive airway and ventilation by blocking the adductor muscles and their ability to open the glottic effectively. (31) This therapy provides temporary relief of symptoms, usually lasting 3 to 6 months. (2) BoNT treatment is generally considered safe, most side effects are benign, transient, localized, and self-limiting. Common side effects include mild injection pain, local swelling and erythema. (50) The use of BoNT for laryngeal injection is contraindicated primarily for neuromuscular disorders and allergies to botulinum toxin. (51)

11.2. Gene therapy laryngeal injection

Gene therapy is an emerging pre-clinical treatment that stimulates the regeneration and repair of injured neurons and laryngeal muscles. This approach involves the incorporation of genes that code for cell growth factors, which promote muscle cell differentiation, proliferation, and neurotrophic factors. These therapeutic genes are injected directly into the RLN, or laryngeal muscles, via vectors and absorbed by muscle cells or neurons. Gene therapy for RLN injury has been investigated in experimental studies using animal models. Injection of the insulin-like growth factor I gene into TA muscles resulted in a larger muscle fiber diameter and an increase in the number of axon-contacting end plates. Additional investigated experiments, involve the injection of adenoviral vector encoding for glial cell line-derived neurotrophic factor (GDNF) following vagal nerve transection, which reduces loss of nucleus ambiguus motoneurons, reduces nitric oxide synthesis, and preserves choline acetyltransferase immunoreactivity, all of which improve nerve recovery. Additional studies that injected GDNF-tagged adenoviral vectors into RLN showed improved nerve conduction velocity, higher vocal fold motion recovery, larger axonal diameter, and remyelination. (52) The limitation of gene therapy in the treatment of BVFP is the inability to prevent synkinesis, a condition characterized by involuntary and undesirable facial movements associated with voluntary facial movements. (53) Further research is necessary to reduce the neurological risk caused by the viral vector injection into the CNS. Despite this, gene therapy could be a promising therapeutic option for VCP.

11.3. Steroid laryngeal injection

Glucocorticoids are natural molecules synthesized within the human body that regulate a variety of physiological, immune, and metabolic processes. Steroid injection is a commonly used treatment for situations where edema may compromise the airways or benign vocal fold lesions. (54) By modifying proinflammatory cytokine secretion, it can decrease collagen deposition and result in reduced fibrosis. Glucocorticoids injection has been shown to reduce the rigidity and vocal strain of hypertrophic vocal fold scars. In addition, it has been proven to increase vibratory abilities and improve voice quality. However, this treatment does not increase the vocal folds volume, resulting in no effect on the prolongation of voice production. (55) In general, steroid laryngeal injection is a safe, accessible treatment option with low complication rates. (56)

11.4. Growth factors laryngeal injection

Basic fibroblast growth factor (bFGF) has shown promise in the treatment of various vocal fold conditions. It can stimulate fibroblast proliferation and increase the synthesis of ECM, increasing hyaluronic acid and matrix metalloproteinase levels while decreasing collagen deposition, resulting in a thicker SLLP. In theory, bFGF can increase tumor vascularity, blood flow and growth. However, repeated treatments are required to achieve the target outcome due to their short half-life. (57)

11.5. Mesenchymal stromal cells laryngeal injection

Laryngeal injections of mesenchymal stromal cells (MSC) have shown promising clinical outcomes in pre-clinical models of vocal fold injury. (5) Characterized by their anti-inflammatory function, MSC produce a significant impact on ECM composition and tissue structure, resulting in healing tissue damage. (43) The goal of this treatment is to improve vocal folds elasticity as well as voice quality. The benefits typically became apparent after 3 months, with no documented side effects. (5)

12. Future directions

The future directions of the field of vocal folds injection are expecting many advances in treatment options. Currently, there is no one optimal material over others for replacing SLLP and one that improves or enhances voice production. Improvements in procedures or equipment, such as delivery methods, the viscosity of materials, or developing articulating cannulas, would allow for improved injection delivery methods and facilitate performing injections in-office setting. Currently, research focuses on optimizing the biomechanical match of injectable materials with the host tissue. Future development of vocal fold injectable materials will likely focus on providing safe products that functionally match the host's viscoelastic properties. (1) Outcome measures such as cellular response, inflammation reaction, and biodegradation should be prioritized for developing new injection materials, as they could have the same downgrades of currently available materials. In addition, another objective should be to address the duration of effect for future development treatments, as the current available treatments offer only temporary solutions. (57)

13. Conclusion

The findings of this study underscore the crucial role of laryngeal injection therapy in the management of vocal fold palsy through discussion and understanding of the anatomical and physiological properties of the larynx and laryngeal injection. Emphasizing advantages like effectiveness and safety compared to invasive surgical methods. While bilateral and unilateral vocal fold paralysis have distinct characteristics, the limited space of the larynx and the vocal folds necessitate a precise approach and evaluation, although the treatment and clinical evaluation can have similarities across these conditions. This study has covered a wide range of available materials and approaches that have evolved to produce better outcomes and address the patient's needs and limitations. In addition to improving voice quality, swallowing, and breathing, laryngeal injection significantly decreases the need for irreversible surgical procedures, which can have a serious impact on life quality. The variability in the duration of the effects of available materials, despite their good results, emphasizes the need for innovation or improvement to develop optimal materials with prolonged treatment effects on the body. Furthermore, because laryngeal injections serve as symptomatic relief therapy, addressing the root cause of vocal fold palsy is essential for the development of more curative treatments and decreasing the prevalence of these conditions.

14. References

1. Mallur PS, Rosen CA. Vocal Fold Injection: Review of Indications, Techniques, and Materials for Augmentation. Clin Exp Otorhinolaryngol. 2010 Dec;3(4):177–82.

2. Yeung W, Richards AL, Novakovic D. Botulinum Neurotoxin Therapy in the Clinical Management of Laryngeal Dystonia. Toxins. 2022 Dec 1;14(12):844.

3. Biello A, Volner K, Song SA. Laryngeal Botulinum Toxin Injection. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK567733/

4. Lyberg-Åhlander V, Rydell R, Fredlund P, Magnusson C, Wilén S. Prevalence of Voice Disorders in the General Population, Based on the Stockholm Public Health Cohort. J Voice Off J Voice Found. 2019 Nov;33(6):900–5.

5. Hertegård S, Nagubothu SR, Malmström E, LeBlanc K. Treatment of vocal fold scarring with autologous bone marrow-derived human mesenchymal stromal cells—first phase I/II human clinical study. Stem Cell Res Ther [Internet]. 2020 [cited 2024 Mar 6];11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7083053/

6. Alwan M, Paddle PM. Vocal Cord Paralysis: Pathophysiology, Etiologies, and Evaluation. Int J Head Neck Surg. 2022 May 21;12(4):153–60.

7. Saran M, Georgakopoulos B, Bordoni B. Anatomy, Head and Neck, Larynx Vocal Cords. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK535342/

8. White AM, Lasrado S. Anatomy, Head and Neck, Thyroid Arteries. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560666/

9. LinkedIn [Internet]. [cited 2024 Mar 6]. Available from: https://www.linkedin.com/pulse/anatomy-larynx-viki-voice-coach

10. Walimbe T, Panitch A, Sivasankar PM. A Review of Hyaluronic Acid and Hyaluronic Acid-based Hydrogels for Vocal Fold Tissue Engineering. J Voice Off J Voice Found. 2017 Jul;31(4):416.

11. LIBRARY AMAP. Science Photo Library. [cited 2024 Mar 6]. Vocal Folds, illustration - Stock Image - C025/6520. Available from: https://www.sciencephoto.com/media/670638/view/vocal-folds-illustration

12. Allen E, Minutello K, Murcek BW. Anatomy, Head and Neck, Larynx Recurrent Laryngeal Nerve. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470179/

13. Philadelphia Ear, Nose and Throat Associates: PENTA [Internet]. [cited 2024 Mar 6]. Anatomy. Available from: https://phillyent.com/anatomy

14. Purves D, Augustine GJ, Fitzpatrick D, Katz LC, LaMantia AS, McNamara JO, et al. Summary. In: Neuroscience 2nd edition [Internet]. Sinauer Associates; 2001 [cited 2024 Mar 6]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10959/

15. Baker E, Lui F. Neuroanatomy, Vagal Nerve Nuclei. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK545209/

16. Larynx - AMBOSS [Internet]. [cited 2024 Mar 6]. Available from: https://next.amboss.com/us/article/T6064S?q=larynx&m=ZhYZcK

17. Zhang Z. Mechanics of human voice production and control. J Acoust Soc Am. 2016 Oct;140(4):2614–35.

18. ALİCURA TOKGÖZ S, SAKA C, AKIN İ, KÖYBAŞIOĞLU F, KILIÇASLAN S, ÇALIŞKAN M, et al. Effects of phenytoin injection on vocal cord healing after mechanical trauma: An experimental study. Turk J Med Sci. 2019 Oct 24;49(5):1577–81.

19. ENVER N, AZİZLİ E, AKBULUT S, ÇADALLI TATAR E, YELKEN MK, ÖZTÜRK K, et al. Inflammatory complications of vocal fold injection with hyaluronic acid: a multiinstitutional study. Turk J Med Sci. 2021 Apr 30;51(2):819–25.

20. Tang SS, Mohad V, Gowda M, Thibeault SL, Wisconsin M. Insights Into the Role of Collagen in Vocal Fold Health and Disease. J Voice Off J Voice Found. 2017 Sep;31(5):520–7.

21. Williamson AJ, Shermetaro C. Unilateral Vocal Cord Paralysis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK535420/

22. Management of Vocal Fold Paralysis II: Role of Injection Medialization [Internet]. [cited 2024 Apr 9]. Available from: https://www.ijhns.com/abstractArticleContentBrowse/IJHNS/27530/JPJ/fullText

23. Salik I, Winters R. Bilateral Vocal Cord Paralysis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560852/

24. Anil HT, Lasya Raj N, Pillai N. A Study on Etiopathogenesis of Vocal Cord Paresis and Palsy in a Tertiary Centre. Indian J Otolaryngol Head Neck Surg. 2019 Sep;71(3):383–9.

25. Onwordi LN, Al Yaghchi C. Airway Glottic Insufficiency. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK538207/

26. Chang WD, Chen SH, Tsai MH, Tsou YA. Autologous Fat Injection Laryngoplasty for Unilateral Vocal Fold Paralysis. J Clin Med. 2021 Oct 28;10(21):5034.

27. Culp JM, Patel G. Recurrent Laryngeal Nerve Injury. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560832/

28. Borgia F, Giuffrida R, Guarneri F, Cannavò SP. Relapsing Polychondritis: An Updated Review. Biomedicines. 2018 Aug 2;6(3):84.

29. Rotshenker S. Wallerian degeneration: the innate-immune response to traumatic nerve injury. J Neuroinflammation. 2011 Aug 30;8:109.

30. Rocha Cabrero F, Morrison EH. Miller Fisher Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK507717/

31. Sahin M, Aydogdu I, Akyildiz S, Erdinc M, Ozturk K, Ogut F. Electromyography-Guided Botulinum Toxin Injection Into the Cricothyroid Muscles in Bilateral Vocal Fold Abductor Paralysis. Clin Exp Otorhinolaryngol. 2017 Jun;10(2):193–202.

32. Vocal Cord Paralysis / Insufficiency Treatments - Medical Clinical Policy Bulletins | Aetna [Internet]. [cited 2024 Apr 9]. Available from: https://www.aetna.com/cpb/medical/data/200_299/0253.html

33. Patel J, Boon M, Spiegel J, Huntley C. Safety of Outpatient Type 1 Thyroplasty. Ear Nose Throat J. 2021 Sep 1;100(5_suppl):608S-613S.

34. What Is the Role of Laryngeal Reinnervation Surgery for Adults with Unilateral Vocal Fold Paralysis? [Internet]. ENTtoday. [cited 2024 Apr 30]. Available from: https://www.enttoday.org/article/what-is-the-role-of-laryngeal-reinnervation-surgery-for-adults-with-unilateral-vocal-fold-paralysis/

35. Salinas JB, Chhetri DK. Injection Laryngoplasty: Techniques and Choices of Fillers. Curr Otorhinolaryngol Rep. 2014 Jun 1;2(2):131–6.

36. Transcutaneous Injection Laryngoplasty: Overview, Indications, Contraindications. 2023 Nov 28 [cited 2024 Apr 9]; Available from: https://emedicine.medscape.com/article/1663452-overview?form=fpf

37. Vocal Cord Injection with Prolaryn Gel with Videostroboscopy (transoral) | Iowa Head and Neck Protocols [Internet]. [cited 2024 Apr 30]. Available from: https://medicine.uiowa.edu/iowaprotocols/vocal-cord-injection-prolaryn-gel-videostroboscopy-transoral

38. Walker K, Basehore BM, Goyal A, Zito PM. Hyaluronic Acid. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Apr 16]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK482440/

39. Kang M, Seo HG, Chung E, Lee HH, Yun SJ, Keam B, et al. Effects of percutaneous injection laryngoplasty on voice and swallowing problems in cancer-related unilateral vocal cord paralysis. Laryngoscope Investig Otolaryngol. 2021 Jul 17;6(4):800–6.

40. Injectable substances for injection laryngoplasty | Iowa Head and Neck Protocols [Internet]. [cited 2024 Apr 9]. Available from: https://medicine.uiowa.edu/iowaprotocols/injectable-substances-injection-laryngoplasty

41. Taufique ZM, Bhatt N, Zagzag D, Lebowitz RA, Lieberman SM. Revascularization of AlloDerm Used during Endoscopic Skull Base Surgery. J Neurol Surg Part B Skull Base. 2019 Feb;80(1):46–50.

42. Truzzi GM, Pauna HF, Bette P, Gusmão RJ, Crespo AN, Semenzati GO. Methods of Fat Tissue Processing for Human Vocal Fold Injection: A Systematic Review. J Voice Off J Voice Found. 2017 Mar;31(2):244.e17-244.e21.

43. Lee DY, Choi YH, Choi JS, Eom MR, Kwon SK. Injection laryngoplasty of human adipose-derived stem cell spheroids with hyaluronic acid-based hydrogel improves the morphological and functional characteristics of geriatric larynx. Biomater Res. 2022 Apr 5;26(1):13.

44. Kinnari TJ, Pietarinen P, Geneid A. Vocal fold augmentation under local anaesthesia using autologous fascia. Clin Otolaryngol. 2018 Jun;43(3):989–91.

45. Belafsky PC, Postma GN. Vocal Fold Augmentation with Calcium Hydroxylapatite. Otolaryngol Neck Surg. 2004;131(4):351–4.

46. ENT & Audiology News [Internet]. [cited 2024 Apr 30]. Vocal cord paralysis: an update. Available from: https://www.entandaudiologynews.com/features/ent-features/post/vocal-cord-paralysis-an-update

47. Jones NN, Song SA. Reinke Edema. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK594275/

48. Admin ENT. The Otorhinolaryngologist - Injection Laryngoplasty [Internet]. [cited 2024 Apr 30]. Available from: https://theotorhinolaryngologist.co.uk/index.php?option=com_k2&view=item&id=361:injection-laryngoplasty&Itemid=718

49. Nigam PK, Nigam A. BOTULINUM TOXIN. Indian J Dermatol. 2010;55(1):8–14.

50. Witmanowski H, Błochowiak K. The whole truth about botulinum toxin – a review. Adv Dermatol Allergol Dermatol Alergol. 2020 Dec;37(6):853–61.

51. McGinty S, Siddiqui WJ. Keloid. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Mar 6]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK507899/

52. Li Y, Garrett G, Zealear D. Current Treatment Options for Bilateral Vocal Fold Paralysis: A State-of-the-Art Review. Clin Exp Otorhinolaryngol. 2017 Sep;10(3):203–12.

53. Guntinas-Lichius O, Prengel J, Cohen O, Mäkitie AA, Vander Poorten V, Ronen O, et al. Pathogenesis, diagnosis and therapy of facial synkinesis: A systematic review and clinical practice recommendations by the international head and neck scientific group. Front Neurol. 2022 Nov 9;13:1019554.

54. Campagnolo AM, Tsuji DH, Sennes LU, Imamura R. Steroid injection in chronic inflammatory vocal fold disorders, literature review. Braz J Otorhinolaryngol. 2008 Nov 1;74(6):926–32.

55. Nozawa M, Takahashi S, Kanazawa T, Kurakami K, Hasegawa T, Hirosaki M, et al. Intracordal injection therapy for vocal fold scarring: Steroid versus basic fibroblast growth factor. Laryngoscope Investig Otolaryngol. 2022 Sep 22;7(5):1465–73.

56. Al-Ali M, Anderson J. The role of steroid injection for vocal folds lesions in professional voice users. J Otolaryngol - Head Neck Surg. 2020 Jul 20;49:50.

57. Imaizumi M, Nakamura R, Nakaegawa Y, Dirja BT, Tada Y, Tani A, et al. Regenerative potential of basic fibroblast growth factor contained in biodegradable gelatin hydrogel microspheres applied following vocal fold injury: Early effect on tissue repair in a rabbit model. Braz J Otorhinolaryngol. 2019 Oct 18;87(3):274–82.