Chapter 9
Office-Based Laryngeal Botulinum Toxin Injection

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9.1 Introduction

Botulinum toxin (BT) is a neurotoxin produced by fermentation of *Clostridium botulinum*. In 1973, Scott et al. introduced BT for medical therapy of strabismus [1]. Since then, BT injection has emerged as a therapeutic modality for other neuromuscular disorders. Botulinum toxin acts by inhibiting the release of acetylcholine at the neuromuscular junction of the targeted muscle leading to temporary chemical denervation and reduction in excessive and/or uncontrolled muscle activity [2]. The heavy chain of the toxin allows binding of the toxin to neurons and penetration of synapses, whereas the light chain is responsible for blocking of calcium-mediated release of acetylcholine [3, 4]. The clinical benefit of BT starts 1–3 days following the injection and usually lasts 3–6 months. The effect is attenuated by resprouting of the terminal axons and the formation of new motor endplates. Resistance to treatment secondary to antibodies production is a concern, and it has been suggested that

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antibody formation may be triggered by BT injections given repeatedly over short intervals and/or when large doses are used. Other factors responsible for immunogenicity include the manufacturing and formulation of the toxin. For that reason, switching to an alternate type of toxin, such as BT-B in cases of resistance to BT-A, might be a solution [4]. Although antibody formation usually is thought to be a concern after 300 mouse units (mu) have been given (total over time), the author (RTS) has seen antibodies develop after as few as 50 mu; and rarely patients have antibodies prior to their first therapeutic injection, presumably due to exposure through food. When a long-term effect is desired (in the absence of antibodies against BT), repeated injections are needed.

There are eight serotypes of botulinum toxin (A to G), the most common of which is type A [5, 6]. In an evidence-based review on the safety and therapeutic effect of Botox, Hallett et al. asserted the efficacious use of different commercial formulations (abobotulinumtoxinA, onabotulinumtoxinA, incobotulinumtoxinA, and rimabotulinumtoxinB) in the treatment of blepharospasm, oromandibular dystonia, torticollis, hemifacial spasm, and focal limb dystonia [6]. Their findings concur with those of Hughes in his report on clinical practice of Botox injection published in 1994 [3]. The author noted the high success rate of Botox injections in comparison to other treatment methods traditionally used in patients with dystonia. For instance, injections of Botox into the trapezius and sternocleidomastoid muscles in patients with spasmodic torticollis were found to be successful in 70–80% of the cases. Similarly, by injecting Botox at various sites of the orbicularis muscle, improvement in patients with blepharospasm was reported in 90% of the cases [3]. Notably, the effect of Botox injection is not only local b ut also central. A "nonclassical" effect on the central nervous system has been suggested by many authors [7, 8]. It includes alteration in the cortical network, change in brainstem interneuronal pathways, and reform in spinal synaptic transmission [9–11].

Given the success of Botox in the treatment of various forms of focal dystonia, the indications for its use have expanded to include laryngeal movement disorders, namely, spasmodic dysphonia, essential voice tremor, paradoxical vocal fold movement disorders or "induced laryngeal obstruction," laryngeal tics, muscle tension dysphonia, and others. This chapter reviews the application of Botox injections in the management of laryngeal movement disorders. The site and dose of injection, as well as associated adv erse effects, are discussed.

9.2 Office-Based Botulinum Toxin Injection in Patients with Spasmodic Dysphonia

Spasmodic dysphonia (SD) is a central neurologic disorder that affects voice and speech. Women are affected more than men with a female to male ratio of 7:1. The peak onset is during the fourth decade of life, and a positive family history is present in 10–12% of the cases [12, 13]. DTY6 (dystonia gene 6) families seem to play a major role, and deletion of three nucleotides in the DYT1 gene has been shown to

be responsible for early-onset focal dystonia [14]. Other predisposing factors include prior history of upper respiratory tract infection and/or stress [12] although causal relationship between these factors and dystonic remain controversial. One out of five patients with SD reports a major stressful life event, a fact that has masked the true etiology of SD for decades. The pathophysiology of SD is multifactorial and includes decreased or loss of motor cortex inhibition, increased plasticity, and abnormal sensory input. Affected individuals have reduced inhibition of the laryngeal adductor reflexes with abnormal sensory gating, all of which leads to disturbance in motor output [15, 16].

Spasmodic dysphonia is a disabling communication disorder that has a profound impact on quality of life. In a review of 60 patients with adductor focal laryngeal dystonia, Stewart et al. reported a VHI-10 score of 21.3 [17]. Affected patients often report difficulty in speech initiation, uncontrolled voice breaks, and marked effort to speak. However, primary vocalization may not be disturbed. Unlike patients with muscle tension dysphonia, in patients with SD singing, yawning, laughing, and crying often are not affected [18], especially early in the disease. Other maneuvers referred to as "sensory tricks" such as chewing also inhibit some of the speech and phonatory symptoms [19]. In adductor SD, the voice breaks are associated with a feeling of choking and strangulation while speaking, particularly when reading all-voiced passages such as "Albert Eat Eggs Every Easter Early in the AM," or when asked to count from 80 to 89. In patients with abductor SD, the voice has breathy breaks associated particularly with prolongation of voiceless sounds such as /p/, /t/, /h/ and /ch/. Voice symptoms also are elicited when patients are asked to count from 60 to 69 or to read a sentence such as "She sells seashells by the seashore. "

Voice tremor is reported in up to one-third of affected patients [12, 18–21] or more. In a review of the demographic data of 718 patients with SD, Patel et al. reported voice tremor in 54.4% of ADSD patients and 32.1% of ABSD patients [22]. Notably, other forms of dystonia such as blepharospasm and cervical dystonia were found in 1.4% and 2.3% of the cases, respectively [22]. Unlike patients with essential voice tremor, patients with SD have no laryngeal tremor at rest and lack pharyngeal and extra-laryngeal muscle tremor. Perceptual evaluation using the GRBAS scale has limited value in patients with SD. As a substitute, the I(I)-NFVO rating scale where the first "I" stands for overall impression, second "I" for the impression of intelligibility, "N" for noise, "F" for fluency, and "V" for voicing is used commonly [23]. Similarly, acoustic analysis using the multidimensional voice program is of limited use in view of the aperiodicity of the vocal signal, variations in voice onset, and high frequency of voice breaks in affected patients. As an alternative, the auditory model-based pitch extractor (AMPEX) has been adopted by some as a robust model that helps characterize and differentiate substitute voices from normal voices [24].

The diagnosis of SD is not limited to perceptual evaluation but relies heavily on laryngeal examination. Task-specific abnormal movements of laryngeal structures usually are seen on flexible nasopharyngoscopy. In cases of adductor SD (ADSD), there is episodic excessive adduction of the vocal folds during phonation, whereas in patients with abductor SD (ABSD), there is excessive abduction with intermittent

incomplete closure of the vocal folds during phonation. The distinction between ADSD and ABSD is not always clear. In many cases, the two entities may coexist, and the clinical demarcation between the two is blurred [25]. Either or both may coexist with tremor, and this combination is called dystonia tremor. It is also important to note the coexistence of compensatory supraglottic muscle tension and/or vocal fold paresis/paralysis in many cases. The use of laryngeal electromyography (EMG) is very useful in excluding other neurologic conditions. Patients with SD typically display a time delay (0.5–1 second) between onset electrical activity of the muscle tested and the onset of phonation [26]. More information on laryngeal EMG findings in patients with SD is available to the reader elsewhere [20].

Treatment of SD is multifaceted. It includes voice/speech therapy, psychotherapy, pharmacotherapy, surgery, and neuromuscular blockade [20]. Voice/speech therapy aims at unloading the laryngeal tension commonly observed in patients with SD, thus reducing symptoms of voice strain and fatigue. The author (RTS) describes successful use of singing to treat SD patients. By attenuating voice spasms during singing and by bridging the singing voice to the speaking voice, affected patients may show marked improvement. Medical treatment using benzodiazepines or phenytoin and psychotherapy to relieve associated stress have been recommended either in isolation or in combination with voice/speech therapy. Surgery has evolved over the last few decades as an alternative especially in recalcitrant cases. Since the introduction of recurrent laryngeal nerve (RLN) sectioning by Dedo in 1976 [27], several surgical options were described among which are RLN crushing by Biller et al. [28], RLN avulsion by Netterville et al. [29], selective section/excision of the thyroarytenoid branch of the recurrent laryngeal nerve by Iwamura [30], and selective denervation/reinnervation of the thyroarytenoid muscle by Mendelsohn and Berke [31]. Other surgical options include endoscopic thyroarytenoid myectomy using cold steel instruments [32], transoral laser thyroarytenoid myoneurectomy [33, 34], radiofrequency thyroarytenoid myothermy [35], and laryngeal framework surgery such as thyroplasty type II with the insertion of a spreading bridge to reduce the forceful closure of the vocal folds and/or thyroplasty type III for relaxation of the anterior commissure [36].

Despite the evolution of surgical techniques in the treatment of SD, the long-term results and high recurrence rates following surgery (recurrent laryngeal nerve section) were discouraging. This spurred efforts to find an alternative treatment. The successful use of neurotoxin in the management of focal dystonia in other parts of the body inspired its widespread usage in patients with SD. Eskander et al. conducted a cross-sectional study looking at the practice in the treatment of ADSD in the Canadian Society of Otolaryngology-Head and Neck Surgery and reported laryngeal BT injections as the most common treatment. The injections were done mostly through the cricothyroid membrane under EMG guidance [37]. Similarly, in the United States, laryngeal BT injection is the most common treatment option in patients with SD. Based on the National Institutes of Health consensus statement, botulinum toxin is a safe and effective treatment of SD among other conditions, when given by health care professionals [38]. Its safety and efficacy depend

partially on the low antigenicity of the botulinum toxin used [20]. In a review of more than 900 patients with SD treated with laryngeal BT injections, Blitzer et al. reported improvement in 90% of patients with ADSD and two-thirds of patients with ABSD [20]. In 2006, Srirompotong et al. reported their experience in the treatment of 37 patients with SD, 25 of whom had undergone BT injection, and reported improvement in 76.8% of the cases at the final stage of treatment. The treatment effect lasted 13.6 weeks on average [39]. Kendall and Leonard investigated the effect of interarytenoid Botox injection in combination with TA muscle injection in the treatment of SD-associated voice tremor. The authors reported better results in those who had both IA and TA injections in comparison to those who had only TA injections. In addition, there was an improvement in most acoustic parameters except for cycle-to-cycle variation in frequency [40]. In 2018, Patel et al. reviewed 548 patients with ADSD, laryngeal tremor, and ADSD with laryngeal tremor, who had undergone 12,771 laryngeal BT injections. The percentage of maximal benefit following BT injection was 88.1% for patients with ADSD and 83.4% for patients with ADSD and lateral tremor. The authors emphasized the effectiveness of onabotulinum toxin A injections into the TA/LCA muscle complex in affected patients (Video 9.1) [41].

The improvement in voice quality following BT injection in patients with SD is attributed to both a local and central effect. BT injection into the intrinsic and extrinsic laryngeal muscles has been shown to result in favorable alteration in laryngeal airflow. Finnegan et al. investigated the effect of BT injection on laryngeal airflow in patients with SD with voice tremor and reported an increase in the mean airflow and a decrease in the coefficient of airflow variation. The latter is indicative of improved stability of laryngeal muscle activity and breathing [42]. Ali et al. investigated BT-induced alterations in CNS activity in patients with ADSD and reported a significant increase in speech-related sensory response in heteromodal sensory areas. The increase in sensory response was commensurate with clinical improvement in voice breaks and percentage aperiodicity. The regional cerebral blood flow (RCBF) was assessed using positron-emission tomography before and after administration of botulinum [43]. The clinical improvement correlated significantly with attenuation in RCBF in motor-associated regions and augmentation in RCBF in unimodal and heteromodal sensory regions associated with oro-motor control.

The outcome of botulinum toxin injection in patients with SD depends on several factors, the most important of which is the dose injected. The effect is believed to be faster when higher doses are used. In a national survey on the use of BT injection in the treatment of SD by experts in the United States, most treating physicians performed bilateral injections with a starting dose of 1.25 IU in ADSD and unilateral injections with a starting dose of 5 IU in ABDSD. The survey included 70 laryngologists who answered a 58-item online survey [44]. Based on the above survey, laryngeal EMG is used by physicians in 87% of patients with ADSD and 67% of patients with ABSD [44]. Other muscles injected include the cricothyroid muscle. The dose varies markedly between patients and with the type of botulinum toxin used and its potency [20]. Another important determinant of the outcome of

BT injection is the ability to target the muscles affected the most. In a review on the clinical application of laryngeal EMG, Sataloff et al. emphasized the added value of laryngeal EMG in targeting the affected muscles and in differentiating between the different forms of SD [45]. In a study of 214 patients with laryngeal dystonia, Klotz et al. showed that difficulty in achieving the desired result was attributed to failure to inject the muscles affected the most. Using fine-wire electromyography, the authors noted that the TA muscle was predominantly affected in ADSD, whereas both the TA and lateral cricoarytenoid muscles are predominantly affected in tremor SD [46]. Maronian et al. reviewed their experience with 81 patients with tremor laryngeal dystonia treated with Botox injection; they used fine-wire electromyography and reported clinical improvement in most patients. The thyroarytenoid muscles and lateral cricoarytenoid muscle were injected in 52% and 48%, respectively. The authors discussed the efficacy of LCA Botox injection in the treatment of these patients [47]. Other factors to be considered in predicting the voice outcome of BT injection are patients' characteristics. Nonbiological factors may contribute significantly to the success or failure of therapy. In a study of 36 patients with ADSD treated with BT injection, Rutt et al. reported that preprocedure education, body position, and stress experienced during the procedure are important factors that can influence the results in 87%, 33%, and 30% of the cases, respectively. The authors stressed the role of patient education before the procedure in improving patient experience and outcome [48]. History of prior surgical treatment is also an important determinant. In a review of 16 patients with ADSD who had undergone nerve section and later BT injection (n-181), Sulica et al. reported less satisfactory results in comparison to patients who were treated primarily with chemodenervation. Nevertheless, there was a significant improvement in voice quality that peaked in 10 days following the injection and lasted 14 weeks, on average [49].

The use of BT in the treatment of SD carries risks and expected adverse effects of which patients should be aware. Preoperative education and counseling are essential for improvement of patients' experience and tolerance of the adverse effects of laryngeal BT injections. Complications reported following BT in the TA muscle in patients with ADSD include breathiness, aspiration of clear fluids, dysphagia, and throat pain. Another rare complication is temporary bilateral vocal fold paralysis. In a review of 352 patients with ADSD who had undergone botulinum toxin injection, Venkatesan et al. reported bilateral abductor paralysis in eight patients, one of whom needed a tracheotomy. The vocal fold paralysis was ascribed to diffusion of the neurotoxin into the posterior cricoarytenoid muscle [50].

SD is a laryngeal movement disorder that can be treated successfully with BT injections. Targeting the affected muscle under EMG guidance helps optimize the outcome. History of prior treatment, site of injection, and dose of BT are important determinants of the success of injection. Patient counseling and education are crucial. Side effects such as breathiness and dysphagia need to be discussed with the patient before intervening.

9.3 Office-Based Botulinum Toxin Injection in Patients with Essential Voice Tremor

Essential voice tremor (EVT) is a neurologic disorder characterized by periodic fluctuation in loudness and pitch that impairs normal communication. Based on the International Parkinson and Movement Disorder Society, EVT is a clinical variant of essential tremor that affects the larynx and pharynx during speech and quiet respiration [51]. The structures commonly affected are the soft palate, base of tongue, lateral pharyngeal wall, false vocal folds, and true vocal folds. Other structures such as the strap muscles and respiratory muscles also may be involved [51]. Essential voice tremor affects women (75–93% of the cases) more often than men, with a mean age of onset at 60 years. Positive family history is reported in 38–42% of the cases [52]. In a clinical study of 34 patients with EVT, Sulica et al. noted a positive family history in 30–50% of the cases [53].

The diagnosis of EVT is challenging because less than one-third of affected patients have tremor of the extremities. This explains the delay in diagnosis of up to 7 years from the time of initial presentation [53]. The diagnosis of EVT relies on subjective and objective evaluation. Visualization of vocal folds and vocal tract kinetic behavior is key for diagnosis [54]. *On examination, tremor is not limited to the intrinsic laryngeal muscles but involves the extrinsic laryngeal muscles as well* [55]. The use of phonatory tasks such as phonating /a/, sustaining the */s/ or whistling may be useful in differentiating EVT from laryngeal dystonia. A delay between voice tremor and laryngeal muscle tremulous activity is observed in many cases*. Bové et al. developed and validated the vocal tract scaling system (VTSS), an assessment tool that helps evaluate EVT and determine treatment efficacy with a high predictive value. The VTSS accounts for various sites of tremor along the vocal tract, including the palate, base of tongue, pharyngeal wall, false vocal folds, and true vocal folds. Both the intra-rater and inter-rater variability are reported to be excellent, with the latter being at least 0.914 [56]. Acoustic/spectral analysis also has been used in diagnosing EVT. Paige et al. investigated the frequency of EVT in 160 patients using computerized peak detection method and reported a median frequency between 4 and 5 Hz, with a normative frequency range of 3.8 to 5.5 Hz [57]. Gamboa et al. in their acoustic analysis of 28 patients with essential tremor found higher jitter and lower harmonic-to-noise ratio values of the vowel /a/ and low intensity and frequency variability while reading a sentence [58]. The acoustic patterns of EVT were also investigated by Lester et al. who showed abnormal fundamental frequency and intensity modulation [59].

The treatment of EVT involves several modalities. Patients often are started on pharmacotherapy using beta-blockers such as propranolol or anticonvulsant barbiturates such as primidone. Nida et al. investigated the effect of primidone in patients with EVT and reported improvement in 14 of 26 patients. However, more than two-thirds experienced side effects, leading to cessation of therapy in half the cases [60]. Justicz et al. reported the effectiveness of propranolol in 18 patients treated with

60–80 mg per day for 2–4 weeks. The authors noted an average change in VRQOL of 9.31 and significant improvement in VRQOL (greater than 10) in 6 of the 18 patients [61]. *Another common treatment is neurotoxin injections. BT injections are offered as the first line of therapy and to patients who are refractory to medical treatment* [62]. In the above study by Justicz et al., 15 patients who were treated subsequently with BT injection reported improvement in their perceptual assessment and VRQOL score. Eighty-nine percent had bilateral injections into the TA/LAC complex, and the average dose used was 3.18 units [61]. In a longitudinal study on the use of BT in the treatment of EVT, Warrick et al. reported a decrease in the frequency and amplitude of tremor during the first week postinjection. Patients also had a decrease in voice effort that was commensurate with a decrease in laryngeal hyperactivity and airway resistance. All patients had bilateral injections into the TA muscle and were evaluated before injection and 2–16 weeks after [63]. The same authors investigated the efficacy of unilateral vs. bilateral BT vocal fold injections in a group of patients with EVT. Using laryngeal EMG guidance, patients were injected with either 2.5 IU bilaterally or 15 IU unilaterally. The authors noted a reduction in tremor and vocal effort that coincided with a decrease in laryngeal resistance in three of the ten patients who had bilateral injections and in two of the nine who had a unilateral injection [64].

Given that EVT is not limited to the true vocal folds, there are many studies on the benefit of BT injections in muscles other than the TA/LCA complex. In 2000, Hertegård et al. reviewed the voice outcome of 15 patients with EVT who had BT injection in the TA, cricothyroid, and thyrohyoid muscles and reported successful treatment in 50–65% of the cases. There was a significant decrease in fundamental frequency variation during sustained vowel production, which corresponded to a subjective decrease in voice tremor [65]. Nelson et al. reported their experience with BT injection in the TA and laryngeal strap muscles in 21 patients with laryngeal tremor, two-thirds of whom had both vertical and horizontal tremor. Using VHI-10 and CAPE evaluation, the authors reported subjective voice improvement in 96% of cases (100% in those who had both TA and strap muscles injection). The mean of improvement per injection was 70%. It is important to note that 62% of their study group had spasmodic dysphonia as well [66]. In another retrospective analysis of 16 patients with EVT, 15 of whom had horizontal laryngeal tremor and 13 of whom had vertical laryngeal tremor, Gurey et al. reported improvement in tremor amplitude following bilateral BT injection into the thyroarytenoid muscles. Patients with vertical tremor had additional BT injections into the strap muscles that were successful [67].

The role of injection laryngoplasty in in the treatment of EVT remains controversial. Van Doren et al. reported improvement in VHI-10 score and subglottal pressure in three of six patients with EVT and vocal fold atrophy who had undergone injection laryngoplasty. Overall, there was improvement in vocal fold function and patient satisfaction in two-third of the cases. The authors discussed the value of vocal fold augmentation in patients with EVT and comorbid vocal fold atrophy or glottal insufficiency from other causes [68]. However, in a comparative study on the utility of injection laryngoplasty in patients with EVT who had undergone BT

injection, Estes et al. reported no significant advantage except for an increase in loudness on perceptual evaluation. Patients had had an increase in airflow following BT which then decreased after vocal fold augmentation. The study was conducted on seven patients who had voice assessment using laryngeal videostroboscopy, acoustic and airflow measures, and perceptual and self-reported assessment [69]. Another promising treatment option in patients with EVT who are refractory to medical treatment and/or BT injection is deep brain stimulation [70, 71]. In a report on five patients with essential tremor, which included a case of essential tremor of the vocal tract, Ruckart et al. reported a significant decrease in VHI-10 score in that patient from 33 to 1 following deep brain stimulation [70]. BT injection may be useful in optimizing the voice following surgery. Future studies on the use of laryngeal BT injections for improving the voice in selected patients' post-deep brain stimulation are needed.

In summary, BT injection is a safe and effective treatment for patients with EVT. The dose of BT should be tailored according to the patients' condition and site of tremor. Various intrinsic and extrinsic laryngeal muscle groups may be targeted. The treatment plan needs to be individualized with extreme care to minimize adverse events.

9.4 Laryngeal Botulinum Toxin Injection in Patients with Vocal Process Granuloma

Vocal process granulomas are benign exophytic lesions usually of the posterior glottis [72]. They were described by Jackson in 1928 as "contact ulcers "of the vocal processes as a result of injury to the overlying mucosa [73]. The injury is perpetuated by endogenous and exogenous factors leading to inflammation of the perichondrium and underling cartilages [74]. Phonotrauma and laryngopharyngeal reflux disease are the main culprits. Phonotrauma can be in the form of a hard glottal attacks, voice abuse, excessively low pitched voice, excessive throat clearing, and coughing [75–77]. The "hammer and anvil" effect between the vocal processes is thought to be the mechanical basis for the formation of these lesions [78]. Exposure of the vocal processes and interarytenoid mucosal lining to the gastric refluxate material is also a detrimental predisposing factor. The resultant irritation and aberrant sensation lead to a traumatic laryngeal behavior that perpetuates the mucosal injury. The vocal process proliferative lesions often raise the suspicion of an invasive carcinoma that is masked by an overlying reactive process [79]. Vocal process granuloma also may result from traumatic laryngeal manipulation and/or prolonged intubation. In 1932, Clausen was the first to report intubation granuloma [80]. When the contact pressure of the tube wall exceeds the mucosa capillary perfusion pressure, ischemia and inflammation occur leading to necrosis and mass formation. The size of the endotracheal tube and the duration of intubation are important factors [81, 82]. Another less recognized cause of vocal process granuloma formation is

glottic insufficiency. In a study of 34 patients with vocal process granuloma, Carroll et al. reported glottic insufficiency in 53% of the cases. The authors alluded to the potential benefit of vocal fold augmentation in patients who are refractory to conventional medical therapy [83].

The clinical presentation of vocal process granuloma varies markedly. While some patients may be asymptomatic, others may present with life-threatening airway obstruction. The most commonly reported symptoms are globus sensation, excessive throat clearing, cough, change in voice quality, voice fatigue, and voice discomfort. Other reported symptoms include odynophagia and otalgia [72, 83]. In rare cases when the lesion is obstructive, patients may complain of shortness of breath and dyspnea [83]. The diagnosis of vocal process granuloma is based on visualization of the lesion on direct or indirect laryngoscopy. The lesion may look exophytic, nodular, hemorrhagic, or ulcerative. A grading system has been suggested by Farwell et al. that stratifies vocal process granuloma into four categories based on the size of the lesion and its appearance [84]. In grade 1 the lesion is limited to the vocal process, sessile, and nonulcerative. Grade 2 lesions are limited to the vocal process but are pedunculated and or ulcerative. Grade 3 granulomas extend beyond the vocal process; and grade 4 is diagnosed when the granuloma crosses the midline when the vocal folds are fully abducted.

The treatment of vocal process granuloma is daunting because of the diversity in clinical presentation and etiology. Several treatment options are described in the literature, with no clear guidelines on how to manage these lesions. In a systematic review of treatment of vocal process granuloma that included 19 studies (8 nonrandomized and 11 retrospective), Karkos et al. reported anti-reflux therapy, speech and language therapy (SALP), and intake of steroids as the most common treatments often used in combination [85]. The large number of treatment alternatives reflects the lack of success with any single modality of treatment. Anti-reflux therapy consists primarily of lifestyle behavioral changes, intake of proton pump inhibitors, antihistamine antagonists, and in rare cases fundoplication [86]. In a retrospective review of 66 patients with vocal process granuloma, 20 of whom were diagnosed with GERD, De Lima Pontes et al. reported resolution of the lesion following anti-reflux treatment in 75% of the cases [87]. In another study by Wani et al. which included 21 patients with vocal process granuloma, the authors reported complete regression in 14 of 18 patients who tolerated PPI treatment and partial regression in 4 [88]. Speech and language therapy (SALT) also has been shown to be efficacious in the treatment of patients with vocal process granuloma. It consists primarily of voice education and voice exercises that aim at reducing the hardness of the glottal attack and other manifestations of laryngeal hyperfunction. Bloch et al. in their study of 17 patients with contact granuloma treated with voice therapy reported resorption of the lesion in 12 and regression in 4. The treatment consisted of relaxation exercises, auditory and kinesthetic feedback, and avoidance of stress/bad phonatory habits [89]. Similar results have been reported in other studies, with a regression rate of 87.5% of the cases [87]. The efficacy of SALT is improved when combined with anti-reflux therapy. Steroid injection has been shown to be effective as well. In a study by Wang et al. on the use of intralesional steroid injection in

patients with vocal process granuloma, the authors reported a reduction in the size of the lesion by 76% or more with complete remission in 60% at 6 months [90].

Conservative therapy using anti-reflux medications and/or SALT is not always sufficient. In patients who are refractory to treatment, or those with large obstructive lesions, surgery is offered as an option. The surgery can be performed using either cold steel instruments or lasers. The overall success rate following surgical removal does not exceed 50% with a high recurrence rate reported. In a study by Ylitalo et al., the recurrence rate in a group of 36 patients who had multiple surgical treatments was 92% [91]. In another study of 23 patients with contact granuloma, Hirano et al. reported resolution in 100% of the cases after 3 interventions. Ten of the 23 patients had recurrence after a single intervention. All patients underwent fiberoptic laryngeal surgery with or without additional laser therapy or steroid injection [92]. Similarly, in a study of 26 patients who underwent a mean of 1.65 ± 1.16 in-office KTP laser treatment, Dominguez et al. reported complete resolution in 73.1% with a median follow-up time of 9.5 months [93]. The incomplete regression of the lesions and the high recurrence rate were attributed to the fact that surgery does not address the cause of contact granuloma.

Laryngeal BT injection has gained popularity over the last two decades as a safe and effective treatment of vocal process granuloma. Botulinum toxin targets the forceful adduction of the vocal folds that is responsible for the mucosal injury or its perpetuation in the posterior glottis. By inducing a temporary paresis of the adductor muscles, the traumatic contact between the vocal processes is inhibited, thus allowing the injured mucosa to heal. The botulinum toxin is usually injected into one of the adductor muscles, the thyroarytenoid muscles (TA), lateral cricoarytenoid muscles (LCA), or the interarytenoid muscles (IA). Nasri et al. was the first to report Botox injection into the thyroarytenoid muscle in six patients with vocal process granuloma [94]. Using the "point-touch technique" described by Green et al. [95], the authors reported complete resolution of contact granuloma in all patients. A total of 10–15 units of botulinum toxin per patient was injected through the cricothyroid membrane or thyroid cartilage. The authors ascribed their therapeutic success to a decrease in the forceful closure of the vocal folds during phonation. The only side effect reported was breathiness which lasted between 2 and 5 months [94]. In 1996, Orloff et al. reported the successful treatment of eight patients with vocal fold granuloma who had undergone at least one previous surgical excision. Four patients needed a second injection, and one needed a third injection. The minimum follow-up was 11 months, and none of the 8 patients had a recurrence. Seven of the eight patients experienced breathiness as a side effect of the treatment. The authors attributed regression of the lesion to neurotoxin-induced temporary paresis which minimized contact trauma and provided a time window for the granuloma to heal [96]. In 2004, Pham et al. reported successful resolution of the laryngeal granuloma (reduction in size by 50% or more) following BT injection into the TA muscle in five of six patients, all of whom had previous surgical resection. Three of the six patients had laryngopharyngeal reflux disease. The patient that did not respond to BT injection had a large obstructive pyogenic granuloma that needed surgical removal. No side effects were noted except for breathiness ($n = 1$) which subsided

[97]. In 2007, Damrose and Damrose reviewed a case series of seven patients with refractory laryngeal granuloma who had undergone vocal fold BT injection (10–15 units) using the percutaneous approach. Five patients had previous surgical excision and three had prior voice therapy. On 2–7 weeks of follow-up, all patients had resolution of their lesions. Hoarseness was reported by all patients and dysphagia was reported by four patients [98].

The high prevalence of breathiness following TA muscle BT injection and other factors have prompted the search for an alternative adductor muscle as a new site of injection. Although the change in voice quality was temporary and self-limited, in professional voice users or subjects who rely heavily on their voice at work, this side effect may be devastating. Another incapacitating side effect of BT injection within the TA muscle is dysphagia. The increased risk of aspiration may require a change in dietary habits. In an attempt to avoid these side effects, numerous authors targeted other laryngeal adductor muscles such as the IA muscle and the LCA muscle. In 2013, Fink et al. reported the use of IA BT injection in eight patients with refractory vocal process granuloma. Five patients had complete resolution of their granuloma, and two patients had partial regression. It is worth noting that four of the eight patients had concomitant intralesional steroid injection. Half the patients experienced mild-to-moderate breathiness which did not affect their daily work. No patient had dysphagia or aspiration. The authors highlighted the value of IA Botox injection in reducing the forceful closure of the vocal processes, with limited effect on the anterior glottis. Moreover, the IA muscle can be identified and targeted percutaneously under direct vision with no need for laryngeal electromyography [99]. In 2015, Yilmaz et al. reported Botox injection into the TA and LCA muscle in 22 patients with different grades of laryngeal granuloma who were followed up for 6 months. The authors noted complete regression in 77% of the cases. The unresponsive cases were treated surgically with additional BT injection [100]. In 2014, Lee et al. conducted a multicenter investigation comparing the treatment outcome of contact granuloma and reported the highest efficacy in BT injection of the TA and LCA (74.2%). The study included 590 patients who were classified as having either primary or refractory contact granuloma [101]. In 2017, Pham et al. reviewed the medical records of 14 patients with vocal process granuloma and reported 2 cases who were treated with botulinum toxin injection within the lateral cricoarytenoid muscles. Both patients had regression in the size of their lesion from grade 3 to grade 1 following one single in-office injection into the LCA muscle thru the cricothyroid membrane under electromyographic guidance. Breathiness was a side effect that lasted only 5 days. The authors ascribed the decrease in the size of the lesion to weakening of the LCA muscle contraction responsible for the forceful closure of the posterior glottis, thereby decreasing the contact trauma at the tips of the vocal processes. The authors also stressed the need for proper patient's selection, i.e., those who demonstrate LCA-dominant closure pattern on endoscopy with forceful point contact at the tip of the vocal process [102]. In 2019, Hamdan et al. reported the efficacy of interarytenoid Botox injection in eight patients with vocal process granuloma who had been treated with PPI without improvement. There was a decrease in

the size of the lesion in four of the eight patients and complete regression in one. The adverse events reported in their study group were breathiness, voice breaks, and aspiration (Video 9.2) [103].

In summary, the treatment of vocal process granuloma should be individualized. The diversity in etiology and the high recurrence rate make treatment very challenging. Although anti-reflux therapy and SALP are the most common treatment approaches, BT injection may be offered to patients as a first line therapy, generally in conjunction with voice therapy and anti-reflux therapy when appropriate. The dose of botulinum toxin and the muscle targeted for injection are based on the type of glottic closure and response to prior treatment.

9.5 Laryngeal Botulinum Toxin Injection in Patients with Vocal Fold Dysfunction

Vocal fold dysfunction is a condition characterized by adduction of the vocal folds during inspiration associated with symptoms of airway obstruction [104]. The term was introduced by Patterson et al. in 1974 [105], following which several anonyms have been reported. These include paradoxical vocal fold movement disorder (PVFM or PVFMD), irritable larynx, hysteric croup, and fictitious asthma, among others. In 2013, the European Society of Otolaryngology, in collaboration with the American College of Surgeons, proposed the term "induced laryngeal obstruction (ILO)" in reference to airway symptoms that occur following a trigger and regress with the cessation of that trigger. The triggers include environmental irritants, cough, exercise, perfume, and other stimuli [106]. Affected patients may invariably complain of intermittent stridor, dyspnea, throat or neck tightness, dysphonia, and difficulty in swallowing. Dyspnea and stridor occur in 73–99% of the cases, and dysphonia is reported in almost two-thirds of the cases [107–110]. The most common cause of dysphonia is the forceful adduction of the vocal folds during inspiratory, which leads to an increase in the collision force between the vocal folds during stridor and hence trauma. The diagnostic criteria commonly used on laryngeal examination are vocal fold inspiratory adduction and/or persistence of a posterior diamond-shaped chink during the attack. More often than not, the laryngeal obstruction is not limited to the glottis but also involves the supraglottic structures. Medialization of the false vocal folds, shortening of the distance between the interarytenoid region and petiole, and abnormal positioning of the epiglottis are observed commonly [111]. The intermittency of the airway symptoms and the normal laryngeal examination between the attacks have led to the use of other tests such as the provocative laryngeal endoscopic test and continuous laryngeal examination (CLE) [108, 112]. The former allows provocation of ILO using an artificial stimulus, whereas the latter facilitates continuous observation of the laryngeal structures throughout the challenge. CLE has allowed diagnosis in patients whose symptoms occur only during peak working capacity and who exhibit normal laryngeal

behavior early during attacks [112]. The immediate visual feedback provided by CL has also revealed abnormal laryngeal behavior at more than one site. Other diagnostic tests used commonly in patients with ILO are pulmonary function test and laryngeal electromyography. Pulmonary function test shows truncation of the inspiratory phase of flow-volume loop, a diagnostic sign of extra-thoracic airway obstruction. A negative methacholine challenge test may support a diagnosis of ILO, whereas a positive one is diagnostic of asthma. The treating physician must be aware of the high prevalence of asthma as a coexisting morbidity in patients with ILO, a fact that may influence the diagnostic utility of methacholine challenge [113, 114]. Laryngeal electromyography is also a diagnostic test useful in differentiating ILO from asthma and from other forms of laryngeal dystonia or movement disorders. Affected patients usually display increased activity in the thyroarytenoid and lateral cricoarytenoid muscles during inspiration even when they are not symptomatic [115]. Several pathophysiologic mechanisms for ILO have been suggested, the most important of which are respiratory dystonia which affects the adductor laryngeal muscles and laryngopharyngeal reflux disease. Other suggested mechanisms include laryngeal hypersensitivity, mechanical predisposition, upregulation in the adductor laryngeal reflex, and psychogenic disorders. Autonomic nervous system dysfunction precipitated by emotional and physical distress also has been suggested as a cause of ILO, very similar to patients with laryngeal hyperfunction [116–121].

Given the multidimensional etiology of ILO, there is no clear consensus on the best management strategy. Numerous treatment modalities are adopted commonly either in isolation or in combination. These include the intake of proton pump inhibitors (PPI) for the control of laryngopharyngeal reflux, speech and voice therapy that focuses on the patient education and control of breathing (respiratory training), cognitive therapy with feedback laryngeal visualization, psychotherapy, and BT injection [122]. BT injection has gained acceptance over the last three decades as a conventional, safe, and cost-effective treatment option for ILO, as well as other forms of laryngeal dystonia and movement disorders [13]. In 1994, Grillone et al. reported the successful use of bilateral vocal fold botulinum injection in seven patients with "adductor laryngeal breathing dystonia." Successful treatment lasted 13.8 months on average but was associated with adverse events, namely, aspiration and change in voice quality [123]. In 2000, Altman et al. reviewed their experience in ten patients diagnosed with PVCM, five of whom were treated successfully with BT injection and two of whom received biofeedback therapy. The authors stressed the value of BT injection as a treatment modality in affected patients [124]. Similarly, Maillard et al. reported a case of ILO treated with BT in whom the injection had obviated the need for intubation and/or tracheotomy. The vital efficacy of Botox injection in the management of acute respiratory distress was highlighted [125]. In a review of 46 patients with PVFMD (another name for ILO), Marcinow et al. stressed the role of TA muscle BT injection in the treatment of patients not responsive to laryngeal control therapy. The authors stressed the sensitivity of post-exertion flexible laryngoscopy in the diagnosis of PVFMD [109]. In 2014, Baxter et al. evaluated the benefits of BT injection in asthmatic patients who suffered from abnormal vocal fold movement. The study was conducted on 11 patients who underwent a

total of 24 injections and showed an increase in asthma control test score and improvement in the size of the upper airway using computerized tomography of the larynx [126]. Similarly, in 2015, Montojo et al. described a 13-year-old girl diagnosed with PVFM who underwent office-based laryngeal injection using BT type A. The patient had complete regression of her symptoms for 5 months [127]. The effectiveness of BT injection in patients with PVFMD also has been reported by deSilva et al. in their review of 13 patients who had 3.85 injections on average per patient. The authors noted a significant decrease in dyspnea severity index score and improvement/complete resolution of dyspnea in 84.6% of the cases [128]. In a retrospective chart review of 40 patients with PVFM, Vance et al. reported improvement in 90% of those who had BT injection, LPR treatment, and/or voice therapy. The authors stressed the effectiveness of BT treatment in affected patients [129].

9.6 Rare Application of Office-Based Botulinum Toxin Injection

9.6.1 Office-Based BT Injection in Patients with Muscle Tension Dysphonia

Muscle tension dysphonia (MTD) is a voice disorder characterized by excessive laryngeal activity. It is a common cause of dysphonia, accounting for one-third of patients presenting with a change in voice quality. MTD is considered primary in the absence of structural or neurologic disorders and secondary in the presence of underlying vocal fold pathology and/or glottic insufficiency [130, 131]. In a study of 100 patients above the age of 40 years, Belafsky et al. noted a higher prevalence of hyperkinetic laryngeal behavior in patients with vocal fold bowing in comparison to those with no vocal fold bowing (17 times more likely) [132]. Precipitating factors for MTD include underlying diseases such as gastroesophageal reflux disease, personality or psychological disorders, and phonotrauma[130]. Patients with MTD often report a change in voice quality described as inappropriatepitch and loudness, associated with neck pain or tightness, vocal fatigue, and sore throat. They are offered a variety of treatment options that include voice hygiene therapy, vocal function exercises, circum-laryngeal manual therapy, medical treatment for reflux disease, and phonosurgery in the presence of vocal fold lesions or structural or neurogenic abnormalities. An alternative rarely offered to patients who are refractory to voice therapy is BT injection (Video 9.3). Rosen and Murry reported a 52-year-old man who presented with severe dysphonia that was attributed to excessive hyperadduction of the false vocal folds during phonation. The voice was described as rough, raspy, and low in pitch. The patient had been treated with voice exercises and hygiene without success. Using the peroral approach, 20 units of BT per were injected into false vocal folds following which the patient had marked improvement in voice quality and resolution of false vocal fold adduction on examination [133].

The results of Rosen and Murry concur with those of Pacheco et al. who reviewed their experience with seven patients diagnosed with refractory muscle tension dysphonia who had false vocal fold Botox injection under general anesthesia. A total of 15 injections were performed with a dose that varied between 30 and 45 units. Of the six patients who were followed up, five had improvement in their voice-related quality of life score. The complications noted were breathiness in two patients and cough in three. The complications were transient and subsided in 1–2 weeks [134].

9.6.2 *Office-Based Botulinum Toxin Injection in Patients with Phonetic Tics*

Phonetic tic is a voice disorder characterized by abnormal laryngeal behavior that results in involuntary sounds such as grunting or throat clearing. Although the primary treatment of phonetic tics is pharmacologic, some patients are offered laryngeal BT injections as an alternative, although its effectiveness remains questionable [135]. In 2004, Porta et al. investigated the effect of vocal fold BT injection in 30 patients with Tourette's syndrome and reported improvement in voice tics in 93% of the cases, with complete resolution in 50% of the cases (n = 15 patients). Despite the fact the majority had hypophonia as an adverse effect of treatment, there was an improvement in overall quality of life and premonitory experiences. Patients were assessed on several occasions over 12 months [136]. The utility of BT (type A) injections also was assessed by Vincent et al. in their case series of two patients. The lowest effective dose used was 0.624 units, and repeated injections were needed to achieve complete resolution of the tic behavior. The author highlighted the successful use of neuromuscular blockade in patients with abnormal laryngeal behavior [137]. Similarly, Kholi and Blitzer reported a 26-year-old male with history of grunting and throat clearing who was treated successfully with laryngeal and f acial BT injections. There was a subjective and objective improvement with a decrease in Yale Global Tic Severity Scale (YGTSS) [138]. Nevertheless, despite the above reports, the effectiveness of BT injection should be investigated further. In a review by Pandey et al. in 2018, the authors noted the uncertain effect of BT injections in the treatment of phonetic and motor tics. The authors also highlighted the high prevalence of adverse events following treatment [139].

9.6.3 *Office-Based Botulinum Toxin Injection in Patients with Parkinson's Disease*

Parkinson's disease is a slowly progressive, neurodegenerative disease characterized by a decrease/depletion of dopamine in the substantia nigra. Affected patients suffer from functional impairment secondary to muscle rigidity and tremor.

Hypokinesia and hyperkinesia are the extreme forms of muscle dysfunction commonly observed in these patients. Speech and voice disturbances are among the plethora of symptoms that prompt medical attention. The phonatory symptoms are ascribed often to restricted mobility of the intrinsic and extrinsic laryngeal muscles, both in the horizontal and vertical dimensions. The most commonly reported symptoms are dysphonia, voice tremor, pitch breaks, delayed onset of phonation, decreased volume, breathy voice, and difficulty in voice projection. Other symptoms include dysphagia and aspiration. On laryngeal examination, there is bowing of the vocal folds, glottic insufficiency, hypo-adduction during phonation, and hypo-abduction during inspiration. Abnormal laryngeal movement is observed in almost 50% of the cases [140]. A multidisciplinary approach is needed to optimize the voice outcome of affected patients. The treatment options commonly offered are medical therapy (levodopa), speech and swallowing therapy, medialization laryngoplasty (injection or thyroplasty), and deep brain stimulation [141–144]. Botulinum toxin injection is beneficial in selected cases. Sachdev et al. reported successful botulinum toxin injection into the posterior cricoarytenoid muscle in 53-year-old man with Parkinson's disease who also suffered from ABSD [145]. The authors attributed the ABSD to neurologic abnormalities in the basal ganglia. Further research on the clinical use of BT laryngeal injections in patients with Parkinson's disease is needed.

9.7 Technique of Office-Based Botulinum Toxin Injection

The procedure starts with identifying the patient, reviewing the patient's chart with confirmation of the diagnosis that requires BT injection, determining vocal fold mobility status on the day of the procedure (especially important in patients who have undergone BT injection previously), and reviewing history of prior treatment including sites and doses of previous injection, if any. The procedure is explained to the patient including expected time to onset of benefits; side effects such as allergic reaction, breathiness, aspiration, and dysphagia; and reasons for possible injection failure such as previously formed antibodies. A signed consent for the procedure is obtained after all patient questions and concerns have been addressed. The planned dose of BT and the muscles targeted for injection are confirmed verbally with the patient and staff. The dose of Botox should be tailored according to the patient's condition and site of the injection. BT can be injected through a flexible laryngoscope with a working channel as shown above, or through the cricothyroid membrane with EMG guidance, as discussed below. A single or multichannel diagnostic EMG machine can be used for EMG needle guidance. A portable, single-channel EMG device that provides only auditory information and single-channel recording was used in procedure illustrated below.

Step 1: BT bottle is checked for the expiration date, and the BT is mixed. The dose planned for the injection is drawn into a syringe (Fig. 9.1).

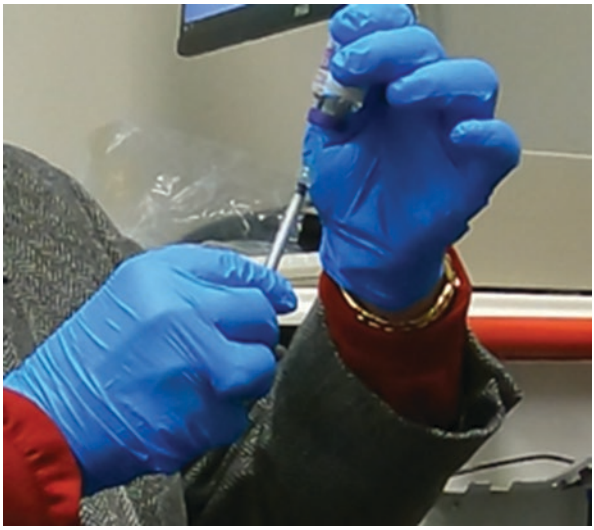

Fig. 9.1 BT injection preparation

Fig. 9.2 EMG wires are connected

Step 2: The patient is placed in a supine position with the neck extended, after using a shoulder roll to improve exposure of the larynx. The procedure can be done with a facemask or tracheotomy in place. If the tracheotomy is high and the neck is short, it may be necessary to remove the tracheotomy tube to permit needle insertion at the correct angles.

Step 3: Surface electrodes are placed on the forehead, chest, or another part of the body away from the neck to ground the patient and help filter background electrical activity. Typically, surface electrodes consist of a metal disk with a diameter of 0.5–2.5 cm (Fig. 9.2).

Step 4: Laryngeal landmarks are palpated (laryngeal notch, laryngeal cartilage inferior border, cricoid cartilage, cricothyroid membrane) for accurate insertion of the electrode into the laryngeal muscles (Fig. 9.3).
Step 5: The neck is cleaned with alcohol pad.
Step 6: The needle electrode is inserted through the skin and into the target laryngeal muscle (Fig. 9.4).

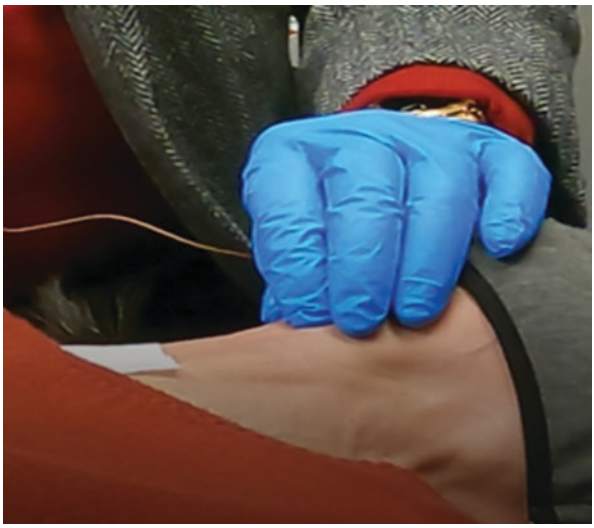

Fig. 9.3 Laryngeal landmarks palpation

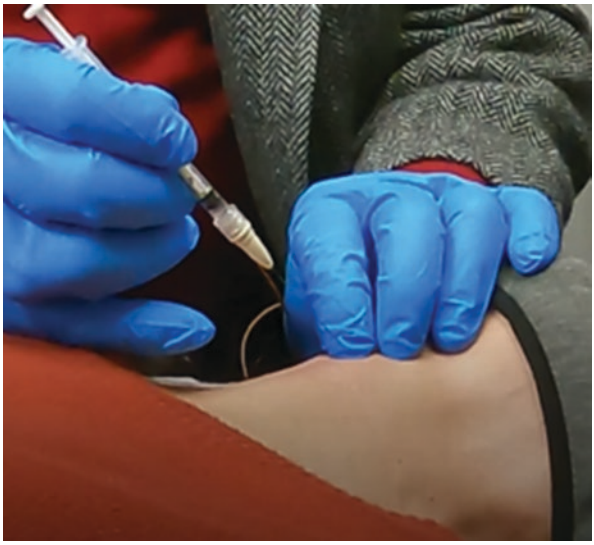

Fig. 9.4 Needle electrode insertion

Fig. 9.5 BT is injected after identifying the intended muscle by vowel signal

Step 7: When the needle is positioned, the patient is asked to perform laryngeal maneuvers (phonatory, respiratory, or swallowing) that require activation of the muscle of interest and relative relaxation of other muscles of the larynx. When the needle is in the correct position, the auditory signal heard through the EMG device's speaker will be increased with the appropriate laryngeal maneuver (Video 9.4).

Step 8: BT is injected through needle electrode once the intended muscle is identified under EMG guidance (Fig. 9.5).

Step 9: Achieving the desired result is confirmed by hearing signal decrease in the laryngeal muscle targeted for the injection as needle tip is surrounded by liquid that separate it from muscle.

Safety Considerations

Current may leak from the electrodiagnostic system and lead to death or injury in a patient by causing ventricular fibrillation. To minimize the risk of this complication, every patient must be grounded, the current leakage from the instrument should not exceed 10 microamperes, and the procedure should be avoided in patients with a cardiac pacemaker.

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