Chapter 9
Botulinum Toxin Therapy for Problems Related to the Gastrointestinal System (Alimentary Tract)

Introduction

Alimentary tract includes mouth, throat, esophagus (the tube that connects the throat to the stomach), stomach and the intestines(gut). Food moves through the alimentary tract and is digested in the stomach and further digested and absorbed in the gut. The alimentary tract (AT) has a muscular wall. Two types of muscles are represented in the AT, striated and smooth muscles. Striated muscles, like those of arm, leg and trunk muscles can be moved at will, whereas smooth muscles' function is not controlled by volition. Most muscles are of the stomach, gut or bladder are of the smooth type; the individual is not usually conscious of their movement.

In the alimentary system, from upper part of the esophagus (the tube that connects the mouth to stomach) to its end (anus, the orifice that through which solid refuse is excreted), there are five strong circular muscles. These circular muscles are called sphincters. Sphincter is a ring shaped muscle that encircles an opening or a passage in the body. In disease conditions, spasm or unwanted contraction of these sphincters can cause pain and discomfort and interfere with the passage of food. The first sphincter of AT is located in the upper esophagus (upper esophageal sphincter -UES) just below the lower end of the throat (pharynx) (Fig. 9.1). This sphincter relaxes during swallowing (initiated by contraction of throat muscles) letting food enter into the esophagus.

The second sphincter is located at the junction of the esophagus and stomach (lower esophageal sphincter- LES). Contraction of this sphincter closes the opening between esophagus and stomach when no food is consumed. During food consumption, and after contraction of the UES, the LES relaxes, opens and lets the food enter into the stomach.

The third sphincter is between the stomach and the small intestine. This sphincter is called pylorus. Pylorus in Greek means gate keeper. From this small circular opening partially digested food passes to the duodenum (first part of small intestine).

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https://doi.org/10.1007/978-3-319-99945-6_9

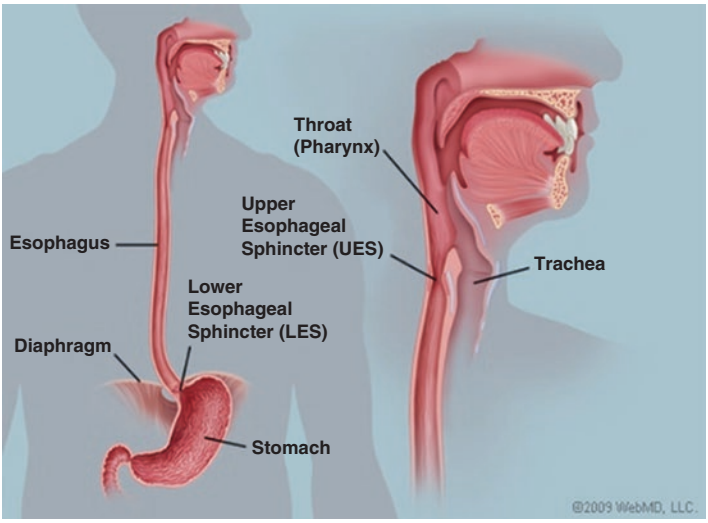

Fig. 9.1 Anatomy of the throat, the esophagus and the two esophageal sphincters -From Mathew Hoffman M.D. Human Anatomy-Digestive disorders- picture of Esophagus – 2009 and 2014 LLC with permission from Web Med

The fourth sphincter controls the opening and closing of the bile duct. Bile which is important for food digestion and is produced in the gall bladder enters the gut through the bile duct. The sphincter that controls the opening and closing of the bile duct is called sphincter of Oddi, named after an Italian physician who first described it (Fig. 9.2).

The fifth sphincter- the anal sphincter -encircles the anus and controls the act of defecation. Relaxation of this sphincter lets the food refuse out of the body.

All these sphincters can be affected and may not function properly if the brain or spinal cord is damaged and the sphincters' nerve supply from central nervous system is interrupted. Common causes of such damages are stroke, trauma, Parkinson's disease and multiple sclerosis. Brain and spinal cord control the function of alimentary sphincters through fine motor fibers. In normal conditions, the function of every muscle in the body (including alimentary sphincters) is maintained through a balance between excitation and inhibition. Brain excites the muscles through excitatory fibers that induce muscle contraction. These fibers release a chemical at their end that excites the muscle; this chemical (transmitter) is called acetylcholine. The inhibitory fibers also have their own transmitter which is different from acetylcholine. For reasons that are not well understood, conditions that commonly damage the brain or spinal cord, damage the inhibitory fibers more often than the excitatory fibers. This tilts the balance towards excitation that gradually keeps the muscles in a state of continuous tightening and contraction. In the limb muscles, this increased muscle tone is called spasticity. The same tightening that affects the limb muscles can affect the function of all 5 above mentioned sphincters of the alimentary tract. Therefore, tight sphincters can interfere with the function of alimentary system at

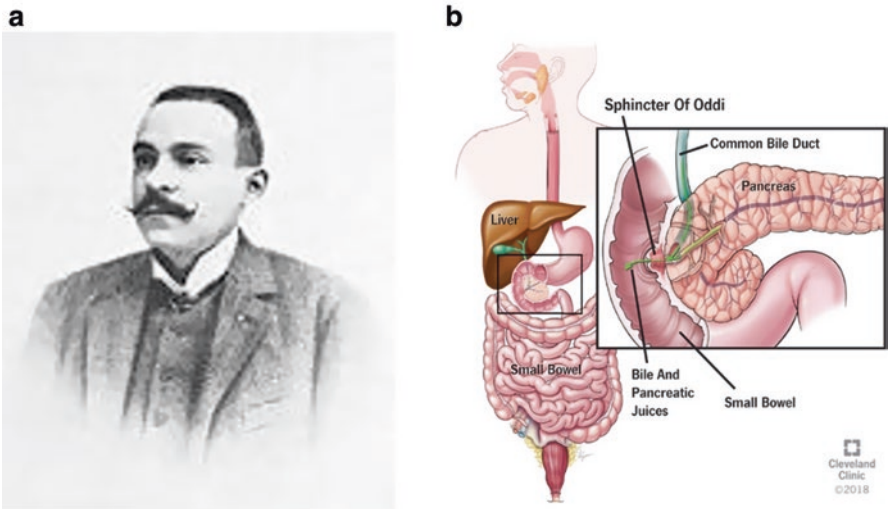

Fig. 9.2 (**a**) Ruggero Oddi, the Italian anatomist that described the bile duct sphincter (**b**) Sphincter of Oddi through which bile and pancreatic ducts gain access to small intestine. Reproduced with permission from Cleveland Clinic

different levels. Botulinum toxin injection into any muscle (striated or smooth) can block the release of acetylcholine from the nerve endings and results in muscle relaxation. Because of this function, injection of BoNTs into the hyperactive muscles has now become a major (and in many cases the first line of treatment) in conditions that cause involuntary muscle movements [1]. This is the basis of using botulinum toxin therapy for treatment of alimentary symptoms related to hyperactive sphincter disorders.

Upper Esophageal Sphincter (UES)

UES is located in the lower end of the throat (pharynx) and is vertically 1 to 1.5 inches long (Fig. 9.1). Its main function is to prevent air from the lungs getting into the throat and prevent food coming back from the esophagus into the throat (reflux) after swallowing. After the initiation of swallowing, UES relaxes and lets the food pass from the throat into the esophagus. The act of swallowing generates a wave of muscle contractions in the esophagus downward that moves the swallowed food or liquid toward the stomach. The medical term for these wave- like contractions of esophageal muscles is peristaltis, a term that also applies to the regular movements of the stomach and gut muscles mixing and moving the food through the alimentary system. A tight UES caused by brain damage is unable to function properly. Patients complain of throat tightness, difficulty swallowing, food getting stuck in their throat. When the food is forced down, it may inaccurately move into the windpipe causing strong coughs.

Treatment of UES tightness includes swallowing exercises, administration of medications and surgery. A large number of swallowing exercises are prescribed by speech therapists for management of UES tightness. These include forced multidirectional tongue movements, jaw opening and closing exercises, and stimulation of the palate with ice-cold spoons. In Shaker exercise, the patient lays flat on the back without a pillow and lifts the head while looking at the toes for 10–15 sec; this exercise is repeated 5–6 times during the day. Other exercises include performing a hard swallow several times a day. In Mendelsohn Maneuver, the individual keeps two fingers against his/her Adam's apple(A'A) and then swallows. The Adam's apple (the frontal protruded cartilage of the neck) moves up during wallowing and comes down after swallowing is over. Patient is instructed to push gently against it and prevent the A'A from coming down after swallowing for a few seconds. This is repeated several times a day.

Medications are not effective in relieving swallowing problems related to the tightness of UES. Balloon dilatation of the constricted sphincter is effective, but the effects are transient. Several surgical procedures have been practiced for improving swallowing problems in this condition. Cutting some of the muscle fibers of this sphincter by surgery offers partial relief, but the procedure has the risk of infection and voice impairment; the latter due to damage to the nerve for the upper part of the windpipe. Endoscopic laser surgery (using a device that visualizes the area), offers a safer approach with fewer side effects.

Botulinum Toxin Treatment of UES Dysfunction

Based on the known effect of botulinum toxins on nerve-muscle junction, i.e. inhibition of the excitatory transmitter acetylcholine, investigators began to look at the effects of injection of BoNT into UES for relief of UES tightness.

The first report on efficacy of Botox in relieving tightness of UES was published in 1994 [2]. The authors injected a total of 20 units of Botox into the cricopharyngeal muscle, a muscle that connects the Adam's apple cartilage in front of the neck to the lower throat muscles and to LES. Five of seven patients had complete relief of symptoms after injection. Dr.Sharzehi and his co-workers review of 2016 covered 200 reported patients with LES tightness in whom the success rate with botulinum toxin injection ranged from 43 to100% [3].

In 2017, Dr. Alfonso and his colleagues published the largest patient series of UES dysfunction treated with BoNT injections [4]. Sixty seven patients with UES dysfunction, were injected with 15–20 units of Xeomin (a BoNT type A with units comparable to Botox)) into the cricophryngeal muscle. The causes of UES in these patients included stroke, trauma and multiple sclerosis. The authors described 52% of the patients as high responders since BoNT injection into the region of LES resulted in >2 levels of improvement in dysphagia outcome severity scale (DOSS). In 67% of the patients, the positive effect of BoNT injection lasted more than 4 months; some of these patients had relief that lasted up to one year. No serious

side effects were noted in the responders. However, two patients who did not initially respond and were reinjected developed pneumonia. The authors emphasized risks associated with reinjection of non-responders. Others reported that swallowing may get worse for a few days following BoNT injection before a sustained satisfactory response that often lasts for months becomes apparent.

Currently, some ear-nose and throat specialists in the US and abroad use botulinum toxin injections into the UES sphincter area for treatment of the associated swallowing problem. The 52% rate of success quoted in the most recent review is substantial if one considers poor response to oral medications and the fact that many patients may not be keen about having surgical intervention. The procedure, however, needs to be done by someone experienced with botulinum toxin injections and one who knows well the anatomy of the throat region.

Tightness of Lower Esophageal Sphincter (LES)– Achalasia

The word achalasia which is of Greek origin means failure to relax (Khalan, Khalasis: relaxing). This entity was first described by an English physician, Thomas Willis, in 1673.

In this condition, LES (Fig. 9.1) fails to relax and allow the passage of food from esophagus to the stomach. Unlike dysfunction of UES which often occurs during the course of well- known neurological problems (stroke, trauma, Parkinson), in most cases of LES dysfunction (achalasia), the cause is unknown. It is now generally believed that achalasia is a neurological disorder due to the failure of nerve cells located in the lower part of the brain (brain stem) that are responsible for both relaxation of the LES and peristalsis of the esophagus. Peristaltic movements of the esophagus push the swallowed food downward toward LES. Loss of relaxation of LES and peristaltic movements of the esophagus leads to a large, dilated esophagus which contains copious saliva and undigested food. This can be easily visualized by radiography following swallowing a large volume of barium. The test will show stagnant barium column in a dilated esophagus and a very narrow and bird-beak shape LES at the junction of the esophagus and stomach (Fig. 9.3). Fluoroscopy (video) of the esophagus can show the absence of peristalsis, the wave like movements that move the food down the esophagus toward the lower esophageal sphincter.

Achalasia is rare and has an incidence of 0. 5–1.63 in 100,000 individuals. The symptoms start slowly with most patients seeking medical attention years after the onset of symptoms (average 4–6 years). The most frequent symptom is difficulty in swallowing which is more prominent for solid food than liquids. Heart burn and regurgitation of food are the next two common symptoms. Smaller percentage of the patients (30–40%) complain of weight loss and chest pain. As the disease progresses difficulty in swallowing becomes a disabling symptom.

The aim of treatment in achalasia is to reduce the tone and tightness of the lower esophageal sphincter. To achieve this goal, two approaches are commonly

Fig. 9.3 Barium swallow test in achalasia showing a bird- beak shaped LES between a dilated esophagus on the left and the stomach (lower right). Form Sharzehi and schey 2018 – Printed with permission from Springer Publisher

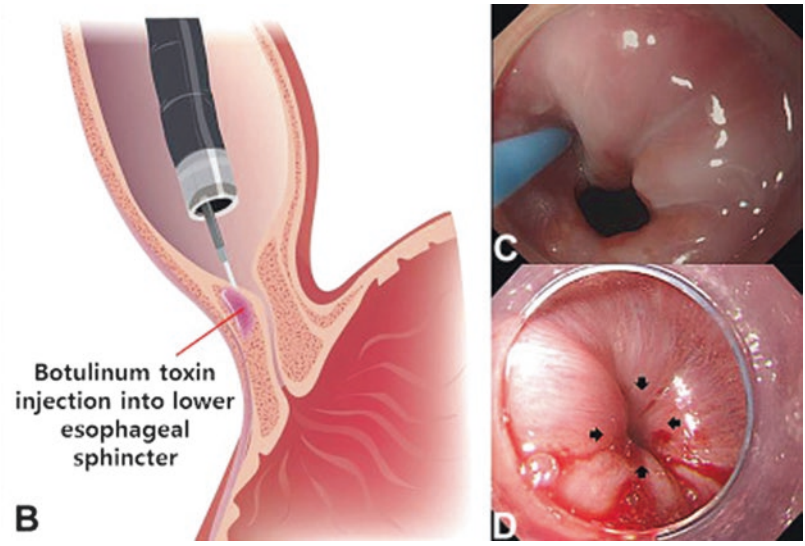

Fig. 9.4 The technique of BoNT injection of lower esophageal sphincter (LES) in achalasia. The needle which is attached to an endoscope, injects the Botox into the contracted LES at the junction of esophagus and stomach. D- shows injection sites into LES into 4 quadrants. From Shim 2014 . Reproduced with permission from Elsevier

implemented. The area of narrowing can be dilated via a procedure called pneumatic (balloon) approach. Alternatively, some of the fibers of the lower esophageal sphincter can be cut (myotomy) through a surgical approach. Although initial success rate is high (85% for dilation and 90% for myotomy), a substantial number of patients demonstrate recurrence of symptoms after 4–6 years.

Medical treatment of achalasia is not very effective. Calcium channel blockers and nitrates have been prescribed with very modest results. It is this medical and surgical treatment restrictions in achalasia that welcomes a new mode of treatment which provides efficacy and has a reasonable safety profile.

Botulinum Toxin Treatment of Achalasia

The first high quality study investigating the efficacy of BoNT injection into LES in achalasia was published by Dr. Pasricha and co-workers in 1995. These investigators have shown that injection of Botox into LES markedly reduces the sphincter pressure, relaxes it and improves the patient's symptoms. The findings were highly statistically significant when compared to the placebo (salt water) injections. Six months after BoNT injection, 14 of 21 patients were still in remission. Botox was injected into LES using endoscopy,a device that inserted into the mouth, moved through the throat and directed to lower esophagus. Four injections, each 20 units, were used covering all four quadrants of the esophagus.

No serious side effects were noted. Other investigators have reported a transient over-relaxation of LES after BoNT injection as a side effect resulting in reflux and heart burn. Although high quality studies of BoNT therapy in achalasia have described no serious side effects, the procedure has a potential of causing serious complications due to the proximity of the injecting needle to vital organs. A single case of death has been reported caused by ruptured lung during LES injection.

The success rate of Botulinum toxin injections into LES in achalasia has been found to be comparable with balloon dilatation and surgery (over 80%). Botulinum toxin injections are believed to have less side effects compared to surgery. Reinjection after 6–12 months is required. Recent studies have shown that two types of botulinum toxin A, Botox and Dysport (see Chap. 5 for toxin types), are equally effective in improving the symptoms of achalasia.

Sphincter of Oddi (SO) Dysfunction

As described earlier, this is another sphincter that is important in proper progression of alimentation. This circular muscle controls an opening through which both bile and enzymes from the pancreas enter the gut, both important players in food digestion (Fig. 9.2). Clinically, tightness of this sphincter can result in three types of symptoms. The most benign symptom is isolated chronic pain, felt below the rib

cage on the right side. The diagnosis is made by measurement of the pressure inside the sphincter. A pressure equal or exceeding 40 mm of mercury is consistent with increased pressure and contraction of sphincter of Oddi (SD). More serious clinical conditions arise from damage to the liver and pancreas due to back up of bile flow or pancreatic enzymes into these vital organs. In these cases, patients may develop severe fatigue, poor digestion and /or jaundice (yellow skin) due to the liver failure, in addition to local abdominal pain and discomfort.

Treatment of SO contraction is difficult. Oral medications are not helpful. Surgery (cutting the muscle fibers of the SO) is also often not helpful and is associated with serious risks such as bleeding, perforation or inflammation of the pancreas. Several pilot studies (not placebo controlled) have shown that injection of Botox into the SO relaxes this muscle and reduces the inside pressure of SO substantially. Pain relief occurs in 50% of the patients following Botox injection; also, some patients do better after surgery if they have Botox injection prior to surgery. Longterm follow ups are needed to determine the role of Botox injections in relieving the symptoms of SO dysfunction.

The effects of Botox injection into SO for patients who have had partial removal of their pancreas due to tumor or inflammation have been explored recently. (tumor, infection). Many of such patients develop a fistula in the pancreas after surgery that complicates their recovery. In one study, injection of Botox into SD significantly decreased development of fistula in the pancreas after partial resection and improved the patient outcome.

Hypertensive Esophageal Disorders

This group of esophageal motility disorders includes diffuse esophageal spasm and nutcracker esophagus. The problem seems to be related to hyperexcitability of the esophageal muscle itself related to decreased activity of inhibitory nerve cells in the brain or enhanced effects of previously described nerve-muscle transmitter acetylcholine. Affected patients complain of difficulty in swallowing (dysphagia), nausea, chest pain and regurgitation.

Medical treatment includes drugs that are commonly used for treating depression such as tricyclic agents and calcium channel blocking agents. Oral nitrate, sildenafil (50 mg) and isosorbide (10 mg) are the next line of treatment. If these measures fail, Botox injections are recommended. Usually, 100 units of Botox is diluted in 4 ml of saline and injected into multiple sites in the lower esophagus, extending from the region of LES to 5 cm and sometimes even farther upward. Between 70–90% of patients respond well to Botox injections with improvements apparent within 30 days. The injections are particularly effective in improving swallowing but have little effect on other symptoms. A repeat injection is required in 6–24 months to maintain the acceptable level of efficacy.

Partial Paralysis of the Stomach -Gastroparesis

Both sympathetic and parasympathetic nervous systems provide innervation to the stomach. Normal function of these nerves which activate and relax smooth muscles of the stomach controls gastric emptying. Gastroparesis is defined by delayed gastric emptying in the absence of a mechanical obstruction. Gastroparesis is much more common in women than men with a prevalence of 38 and 9.6/100,000, respectively [5].

The symptoms of gastroparesis include nausea, vomiting, bloating, excessive fullness after eating, weight loss, abdominal pain and early satiety. Patients may ignore the mild early symptoms for a longtime before seeking medical care. The diagnosis of gastroparesis is made most efficiently by a 4-hour gastric emptying scan.

In approximately, half of the patients with gastroparesis, despite modern medical work up, the cause remains elusive. Common diseases associated with delayed gastric emptying are diabetes, Parkinson's disease, multiple sclerosis, surgical or accidental injury to the vagus nerve (a part of the parasympathetic nervous system) that contracts the stomach muscles and controls the function of pyloric sphincter- circular muscle that controls opening of the stomach into the gut. Movements of the stomach and control of the pylorus are not under conscious control. Excess of certain medications also can cause delayed stomach emptying; most notable among these medications are high doses of narcotics and certain drugs that are used for treatment of Parkinsons disease (Dopamine agonists).

Treatment of delayed gastric emptying starts with dietary counseling and nutritional management. In advanced cases, feeding may have to be done via a tube that delivers food directly to the first part of the gut through a hole opened in the abdomen. The most effective medication for improvement of gastroparesis is a drug called metoclopramide (Reglan) that reduces the effect of dopamine. Surgical treatment focuses on cutting the muscle fibers of the pylorus, electrical stimulation of the stomach or even, in severe cases, removal of the stomach. Many patients remain unsatisfied with the results of these medical and surgical treatments.

The first data on the use of Botox injections in gastroparesis was published in 2002 [6]. Injection of 100 units of Botox into the pylorus (the sphincter between the stomach and the first part of the gut) in patients with gastroparesis secondary to diabetes has improved the symptoms of 50% of the patients as well as showing improvement of the gastric emptying tests. In some studies, the dose was increased to 200 units. Younger patients, women and those patients with unknown cause of their gastroparesis responded better to Botox therapy. The response usually lasts 4–5 months.

Unfortunately, a couple of high quality studies that compared the results of Botox injections with placebo, despite showing improvement of gastric emptying tests, failed to show substantial improvement in patients' symptoms. Furthermore, some reports claim that stomach lining may change and harden after Botox injections, the long-term effects of which are not clear. Due to these issues and concerns,

currently, Botox injection into pylorus remains a debatable approach for treatment of gastroparesis. Some specialists practice it, whereas others refrain from use of Botox for management of gastroparesis.

Anismus – Painful Contraction of the Anal Sphincter and Nearby Muscles

In this condition, external anal sphincter and the muscle attached to it (puborectalis muscle) that connects pubis to rectum, develop high tone and interfere with defecation. In many cases of anismus, instead of relaxing at the initiation of defecation, anal sphincter and puborectalis muscle (PR) contract and make defecation painful and uncomfortable. Anismus can result from surgery of the ano-rectal area, hysterectomy, trauma to the region and even stress but, in many cases, the cause remains undetermined.

Treatment of anismus is difficult. Soft dietary regimen and improving stress is helpful in some patients. Special biofeedback sessions have been reported to help but, success is limited. In severe cases, surgery is recommended. Cutting some fibers of the sphincter and PR muscles reduces the tightness of these muscles and can provide relief in over 50% of the patients. Surgery, however, carries the risk of fecal incontinence and infection.

Application of botulinum toxin therapy for treatment of anismus was first reported by Dr. Hallan and his associates in 1988; they reported significant improvement of constipation in seven patients [7]. In a review of the subject in 2016, Hany Emile and coworkers revealed 11 publications on this subject [8]. The average rate of success was 77% after the first injection. Approximately 45% of the patients were still satisfied 4 months after treatment. The incidence of side effects was 7% and included two patients with fecal incontinence (mild and transient) and one with rectal prolapse. The side effects with Botox injections are, in general, lower than that of surgery, but treatment needs to be repeated in over half of the patients every 4–6 months. Both Botox and Dysport (another type A botulinum toxins) were found to be effective in treatment of anismus. Injections are performed using a thin 27.5 or 30 gauge needle following application of local anaesthesia. The use of electromyography (which shows the electrical activity of the muscle) or ultrasound which visualizes the muscle, add to the procedure's accuracy. For Botox, most clinics use a total of 100 units, often divided between anal sphincter and the PR muscle. Injections are done at multiple sites into the muscle.

Anal Fissure

Anal fissure is a tear in the skin of the anal area usually related to increase pressure of the anal sphincter. The torn area leaves a small ulceration and causes significant pain and discomfort during bowel movement**.** Anal fissures can develop acutely or

gradually. Once developed, the healing is difficult due to spasms of the anal sphincter which pulls apart the edges of the fissure exposing the area to inflammation/infection. Passage of hard stool, chronic diarrhea, prolonged vaginal delivery and anal sex are among common causes of anal fissure. Local pain, local bleeding, skin irritation and persistent itch are common complains of the affected patients.

First line of treatment is loosening the stool by using diets high in fiber and drinking lots of water. Taking Sitz baths several times daily helps local discomfort. Application of local analgesic creams such as lidocaine jelly (2%) and local creams that make blood vessels relax (vasodilators); nifedipine and nitroglycerin are helpful in management of anal fissure. Persistent and unresponsive anal fissures will require surgery which includes cutting the fibers of anal sphincter in order to make it relax. The procedure is helpful but has a high incidence of fecal incontinence specially in elderly patients and women with multiple childbirths.

Botox injection into the anal sphincter, aiming to relax this sphincter and for management of anal fissure was first described by Drs Jost and Schimrigk in 1993 [9]. Injection of a small amount of Botox (2.5 units) into the external anal sphincter improved the patient's symptoms and helped healing of the anal fissure. Subsequent studies recommended higher doses of 10–20 units. A high quality study (comparing the effect of Botox with placebo) have shown that patients who received Botox injections demonstrated 5 or more times symptom improvement and healing of the anal fissure compared to placebo [10]. Another study of 100 patients with anal fissure demonstrated that patients who received Botox injections into the anal sphincter had significantly less incidence of fecal incontinence compared to surgical sphincterectomy; 7% verssus 33%) [11]. Botox injections need to be repeated every 4–6 months. Botox therapy for management of anal fissure is, therefore, effective and remains a good alternative for patients who do not want surgery or those who are at high risk for development of fecal incontinence after sphincter surgery.

Alimentary Problems Related to Tongue Dyskinesia (Involuntary Movements).

Involuntary movements of the tongue are seen most commonly following exposure to certain medications which interfere with the action of an organic chemical called dopamine. Dopamine is present in abundance in brain cells and contributes to the function of motor system. Drugs that block the action of dopamine are now widely used in psychiatry for treatment of schizophrenia and mood disorders. Unfortunately, chronic exposure to these drugs may damage brain cells and causes involuntary movements (tardive dyskinesia). Sometimes these movements are short-lived; sometimes they can persist for a long time, even for life. Involuntary movements of the tongue are often associated with involuntary movements of the face and lips. Tongue movements are often multidirectional, side to side, rolling and sometimes protruding. Involuntary tongue movements are also seen sometimes in certain neurological disorders that involve the brain.

Treatment of tongue movements in tardive dyskinesis(often related to chronic use of neuroleptic drugs) is very difficult. In lucky patients, the movements are self-limiting and disappear within days or months after onset. For those with persistent tongue movements, a drug called tetrabenazine which works on the dopamine system offers partial help.

Injection of botulinum toxins into the tongue can slow down the tongue movements and improve patients' alimentation as well as speech. Recent studies have shown that injection of the tongue in tardive dyskinesia by diminishing the tongue movement can significantly improve the patients' quality of life [12]. The treatment, however, is risky and over dosing can lead to tongue paralysis for 2–5 months causing significant feeding problems. In experienced hands, however, most patients are happy since reduction of involuntary tongue movements improves alimentation and quality of life. I use a ½ inch or ¾ inch long needle (gauge 27.5 mm) through a lateral approach. If using Botox, a starting dose of 5 units/side is usually effective and pleases the patient (although the tongue movements may not totally cease). The dose may be increased to 7.5 units per each side of the tongue in subsequent injections. The effect of Botox usually lasts 3–4 months.

Conclusion

Hyperactivity of sphincter muscles can cause problems with passage of food through different parts of the alimentary system. Botulinum toxin injections by reducing sphincter's muscle tone can help proper passage of food and improve patient's alimentation. Botulinum toxin therapy is effective in management of anal fissure. In medical disorders that result in involuntary tongue movements, injection of botulinum toxin into the tongue can reduce movements and improve the patients' quality of life.

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