Chapter 8
Botulinum Toxin Treatment of Bladder and Pelvic Disorders

Introduction

Bladder functions through the actin of its muscles. Bladder muscles like any other muscle in the body, respond to nerve signals that come from the brain and spinal cord. Botulinum toxins block the release of neurotransmitters at nerve-muscle junction. Neurotransmitters are chemicals that convey the electrical message of the nerve to the muscle and activate the muscle. In human, the main neurotransmitter of nerve-muscle junction is acetylcholine that activates all skeletal muscles as well as visceral muscles such as those present in the bladder. Clinical research and experience over the past 15 years have proven the efficacy of botulinum toxin injection into the bladder wall in improving bladder overactivity problems. These bladder overactivity problems are either due to damage to the bladder nerves such as seen in spinal cord injury or multiple sclerosis or they may have unknown causes. The former is called neurogenic detrusor overactivity (NDO). Detrusor muscle is the main bladder muscle that participates in bladder filling and emptying. The latter bladder condition is termed simply over active bladder (OAB) or idiopathic (cause unknown) overactive bladder IOB.

Botulinum toxins are also effective in relieving pelvic pain in both genders due to their blocking effect on the pain neurotransmitters. Limited data indicate that pain generated by inflammation of the bladder (interstitial cystitis) also responds to injection of botulinum toxins into the bladder wall.

Botulinum Toxins

Botulinum toxin is produced by a form of bacteria called clostridium botulinum and ingestion of a large amount of the toxins produced by these bacteria leads to the serious illness of botulism. The history of botulinum toxin's discovery as a

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treatment agent when prepared in an injectable and safe form is presented in detail in Chap. 1. There are seven serological types of the toxin (A to G), of which, types A and B are in clinical use due to their long duration of action. Three type A and one type B toxin have been approved by FDA for use in the US. The type A toxins have trade names of Botox, Xeomin and Dysport whereas the trade name for the type B toxin is Myobloc in US, Neurobloc in Europe. The propriety name as well as differences and similarities between these toxins are described in Chap. 3.

Because of the powerful effect of botulinum toxins on nerve- muscle junction (details of the mechanism is described in Chap. 2), over the past 30 years, botulinum toxins have developed as drugs of first line for treatment of several hyperactive movement disorders. Botulinum toxins are now approved by FDA for treatment of blepharospasm (forced and repeated eye closures due to overactivity of eyelid muscles), hemifacial spasm (involuntary spasm of the facial muscles on one side) and cervical dystonia (a hyperactive condition causing neck jerks and abnormal neck postures) [1]. In addition, through the same mode of action (blocking the nerve-muscle junction), botulinum toxins' role has now been established as a major mode of treatment for improving and reducing muscle tone and muscle spasm (spasticity) which occur after stroke or after brain or spinal cord injury [2].

The above mentioned positive results with botulinum toxin therapy in a variety of medical conditions characterized by muscle overactivity have encouraged neurologists and urologists to look into the potential use of botulinum toxins for management of bladder dysfunction related to the overactivity of the bladder's detrusor muscle.

Physiology of Bladder Function and the Role of Detrusor Muscle

In health, human kidneys generate 800 to 2000 milliliters of urine per 24 h. The urine that is generated from the kidneys is carried to the bladder by two tubes called ureters (Fig. 8.1).

The ureters connect the kidneys to the bladder where they insert into the posterior aspect of the lower and narrowed part of the bladder called trigone (Triangle). The drainage of the urine to the outside from the trigone is through a hole that opens into a single tube called urethra. Urethra is short in women 1.5 cm and longer in men (10 cm) since it goes through the length of penis.

The bladder is an ovoid shape structure, located in the lower part of the pelvis. The wider part of the bladder is located on the top, while the narrower part is at the bottom (Fig. 8.2). Storage and emptying of the urine are managed by three essential muscles:

1. Detrusor muscle (Fig. 8.2): This is the main muscle of the bladder wall which while relaxed allows the bladder to expand and store urine; its contraction is essential for the drainage of urine.

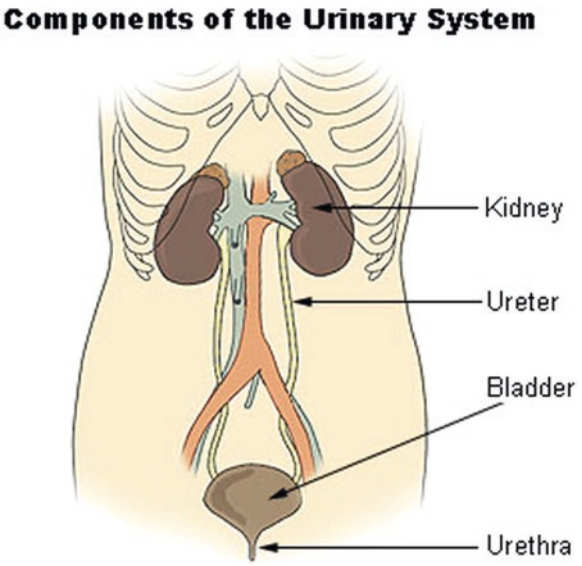

Fig. 8.1 Kidney's, ureters, bladder and urethra. From Wikibooks

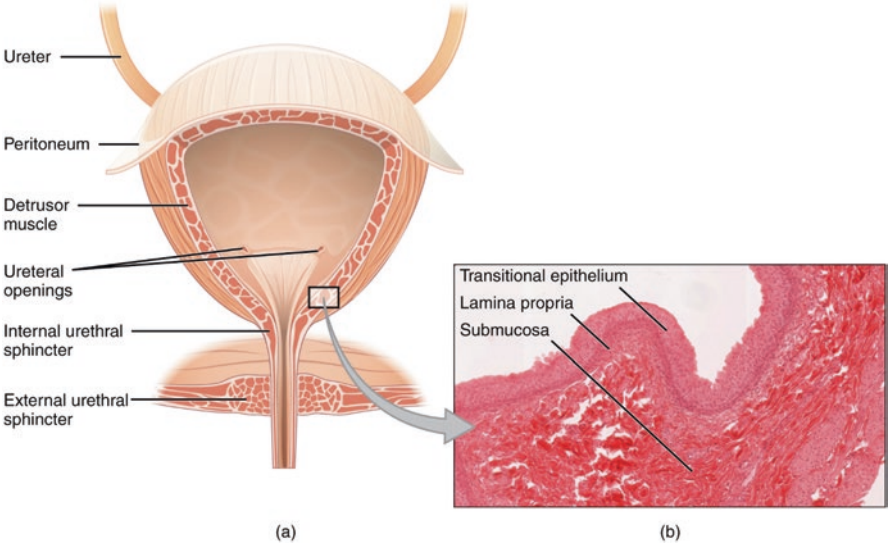

Fig. 8.2 Bladder: base, trigone, detrusor muscle, internal and external sphincters. From https://upload.wikimedia.org/wikipedia/commons/d/dc/2605_The_Bladder.jpg

2. Internal urinary sphincter: This small muscle which is around the neck of the bladder contracts during urine storage and relaxes during micturition letting the urine out of the bladder.
3. External urinary sphincter: this sphincter is located further down on the path of urine drainage, and its function is similar to that of the internal sphincter. However, it is under voluntary control.

The detrusor and internal urinary sphincter are special types of muscles called smooth muscles that are innervated by the autonomic nervous system (sympathetic and parasympathetic), and, hence, are not under voluntary control. The external sphincter, has a structure similar to other muscles of the body referred to as striated muscle and is controlled by volition.

During filling of the bladder, the pressure inside the bladder is constantly sensed by the nerve cells located on the surface of the detrusor muscle. When the bladder pressure reaches a certain point, these nerve cells signal filling of the bladder to the nerve cells located in the spinal cord and brain, which in turn command the release and drainage of urine to bladder muscles. The detrusor muscle contracts and pushes the urine towards the trigone, while the internal sphincter relaxes and lets the urine out toward the external sphincter. At this time, the urgent need for micturition is fulfilled by voluntary relaxation of the external sphincter that pours the urine into the urethra for drainage. The storage and drainage of urine requires proper timing and synergy between detrusor muscle and the two sphincters. In certain neurological conditions, synergy between these muscles does not take place (detrusor -sphincter dyssynergia); this leads to urinary retention. Overactivity or underactivity of detrusor muscles is also the cause of urinary symptoms such as urinary incontinence or retention. Detrusor overactivity is seen in neurological disorders (neurogenic detrusor overactivity -NDO), but sometimes the cause remains undetermined (overactive bladder – OAB). Detrusor underactivity or paralysis of detrusor muscle, occurs in severe spinal cord injury and is not responsive to botulinum toxin therapy.

Neurogenic Detrusor Overactivity (NDO)

Neurogenic detrusor overactivity is the most common type of bladder dysfunction in multiple sclerosis and partial spinal cord injury. Approximately 70% of patients with multiple sclerosis and bladder dysfunction complain of impaired quality of life. Control of bladder function takes place at several levels in the central nervous system: spinal cord, lower part of the brain (brain stem- Pons) and cortex of the brain where the large nerve cells are located. Multiple sclerosis and spinal cord injury damage the nerve cells and nerve fibers that control bladder function. The result of this damage is increased excitability of the fibers that descend from the brain to the bladder and provide nerve supply of the detrusor muscle. This is similar to what happens to other muscles of the body that become overactive in these two conditions whereby patients demonstrate increased reflexes. The term reflex bladder is also used sometimes to characterize overactivity of the bladder's detrusor muscle in NDO.

The symptoms of NDO consist of urinary urgency, urinary frequency and inability to hold urine (incontinence), caused by involuntary and abnormal contractions of a hyperactive detrusor muscle. Urinary urgency (desire to urinate) is the most common symptom and half of the people with urinary urgency have- urge incontinence-wetting themselves during the urge to urinate.

Neurogenic detrusor overactivity often leads to decreased bladder capacity and to residual urine with incomplete bladder emptying. Many patients experience discomfort at the time of urination. These symptoms make the patient prone to developing recurrent bladder infections. Furthermore, increased detrusor pressure can cause backing of urine, dilation of ureters (hydronephrosis) resulting to subsequent damage to the kidneys.

Conventional treatments of neurogenic detrusor overactivity include bladder training, pelvic floor exercises and medications. Among general measures, losing weight in overweight patients and avoiding drinking excessive tea or coffee are often recommended. Bladder training is usually a 3–12- week course that includes different behavioral approaches such trying to delay voiding to void when feeling urge to urinate. Patient starts with 5–10 min deferral, gradually extends delaying time to several hours. This may not be successful in some patients since it requires the ability to tighten the pelvic floor. Scheduling regular voiding times even in the absence of urge to void is also a part of bladder training. Pelvic floor exercises aim to strengthen muscles of the pelvic floor which are located in the proximity or are attached to the bladder (Fig. 8.3). The most common exercise is known as kegel exercise, usually taught to the patient by the physician or a physical therapist. It may take up to 8 weeks before giving any results.

Medical therapy is focused on "urge incontinence" which is the most disturbing symptom. The drugs that are used for treatment of urge incontinence are usually in

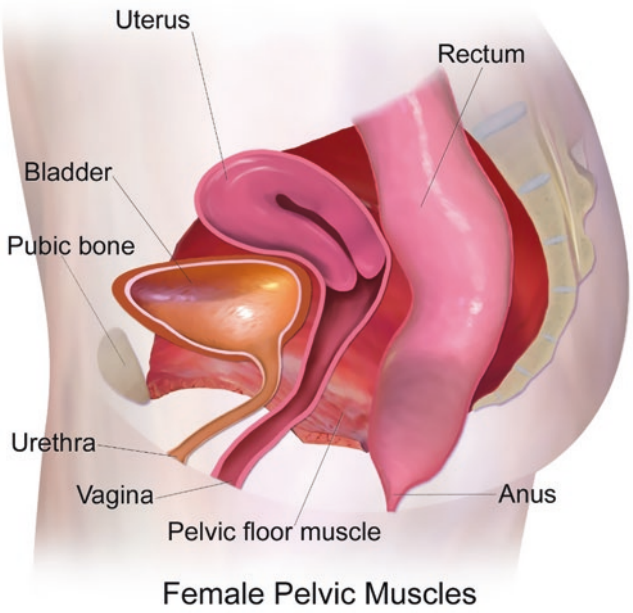

Fig. 8.3 Position of the bladder and pelvic floor muscles- From Wikimedia commons licensed under creative commons attribution

the category of anticholinergics since they block the action of acetylcholine- the previously mentioned neurotransmitter that activates muscles after receiving the nerve signal. Several drugs of this category are available in the market under different trade names such as Detrol and Ditropan. Dryness of the mouth, dryness of the eyes and constipation are common side effects. Elderly patients may experience impairment of memory and confusion. Unfortunately, long-term effects of medications in treatment of overactive bladder related to nerve damage is disappointing. Research have shown that within 2 years after initiating the treatment, half of the patients stop taking these medications either due to inefficacy or due to undesirable side effects [3].

Botulinum Toxin Treatment of NDO

In 2000, Schurch and his colleagues first demonstrated the effectiveness of Botox injections into the bladder wall in patients with detrusor muscle overactivity. Seventeen of their 19 patients completely regained urinary continence 6 weeks after treatment and, in 11 patients, continence of urine persisted for 36 weeks after a single session of injections. Furthermore, they have shown that patients' maximum bladder capacity increased up to 482 milliliters.

In 2010, FDA approved Botox injections into the bladder wall for management of NDO symptoms based on two large multicenter and double- blind studies (both doctor and patients unaware of the type of injection, toxin or placebo) consisting of 217 and 416 patients affected by multiple sclerosis and/or spinal cord injury. These carefully crafted studies which also compared the effect of 200 units of Botox with 300 units, demonstrated significant reduction of incontinence episodes after Botox injections as well as marked improvement of patients' quality of life as measured by standard quality of life rating scales [4–6]. Furthermore, Botox injections were safe and no patient developed any serious side effects. As 200 units was as effective and had less side effects compared to the 300 units, the FDA approval was issued for the 200 unit dose. Subsequently, several follow up studies have demonstrated maintenance of efficacy after repeated injections of Botox over years (3–6 years) with the time interval between injections varying from 7 to 11 months.

The main side effect of Botox treatment of neurogenic detrusor overactivity is urinary retention observed in 9% of the treated patients which will require daily self-catheterization. For many patients with spinal cord injury or multiple sclerosis, this may not be a major issue since they are already in that stage. The need for self-catheterization after Botox injections, however, decreases with the passage of time. A recent follow up study of 227 patients with NDO have shown that the need for self-catherization in the third and fourth year after initiation of Botox therapy dropped to 8% and 0% respectively [7]. Increased urinary tract infections were noted after Botox injections in patients with multiple sclerosis, but not among patients with spinal cord injury.

Injection Technique

For injections, 100 units of Botox are diluted in 10 cc of normal saline and injected via an endoscope into the bladder. An endoscope is a device which can visualize the bladder wall and maneuvered inside the bladder. Injections are superficial and on the surface of the detrusor muscle at multiple sites almost in a grid-like pattern**.** The initial FDA approved protocol spares the trigone of the bladder and recommends a total dose of 200 units of Botox (Fig. 8.4).

In recent years, several authors have recommend including the trigone of the bladder in the injected area since this region of the bladder is rich in nerve fibers; in the experience some investigators inclusion of the trigone in the plan of injection provides better outcome. Dr.Smith and his colleagues from Baylor College of Medicine in Houston, Texas include the trigone and adjust the dose based on the type and severity of the bladder dysfunction. Their protocol for patients with mild symptoms recommends 9 to 10 injection sites with a total Botox dose of 100 units. For patients with severe symptoms who are already catheterizing themselves, 30–40 injection sites are recommended with a total Botox dose of 200 units (Fig. 8.5).

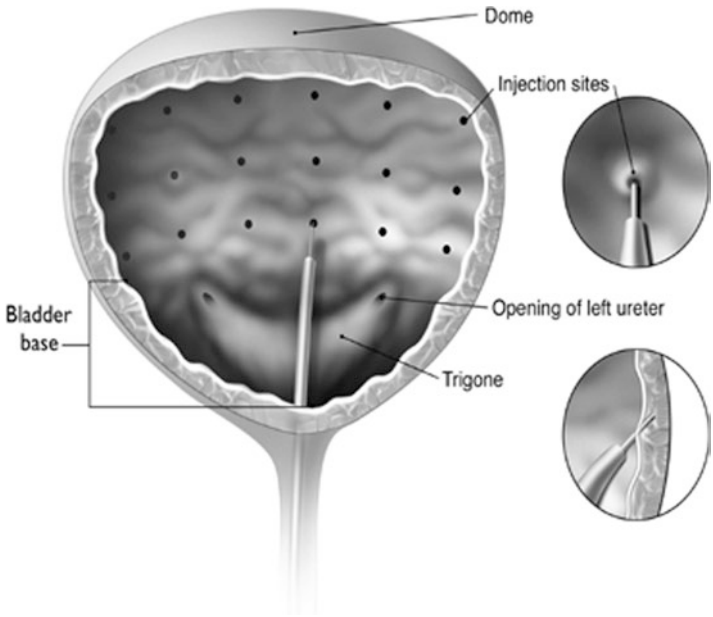

Fig. 8.4 Site of Botox injections for overactive bladder sparing the trigone. From Talab et al. Botulinum Toxin Treatment in Clinical Medicine. Jabbari B(Editor). Printed with permission from Springer

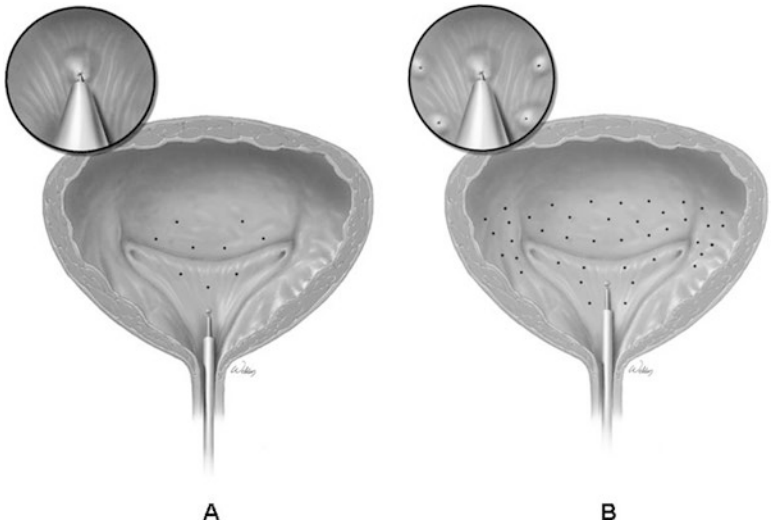

Fig. 8.5 Technique of bladder injection. (**a**) for patients with mild symptoms (**b**) for patients with severe symptoms. From Smith and Chancellor. Seminars of Neurology 2016. With permission from publisher-Thieme

Overactive Bladder of Unknown Cause (OAB)

This category includes patients with undetermined cause of bladder overactivity. Among adults a prevalence of up to 16.9% has been reported in general population increasing to 30% among those of 75 years or older [8]. The symptoms of OAB are very similar to those of NDO; mainly urinary urgency, frequency and incontinence. These symptoms are managed similarly with bladder training, pelvic floor exercise and anticholinergic medication. Myrbetrig is a newer drug in the market that enhances the effect of adrenergic (adrenaline enhancing) system and can alleviate some of the symptoms of OAB. Its side effects consist of allergic reactions, nausea and headaches as well as raising the blood pressure. Like NDO, failure of medical therapy is not uncommon in OAB. Also, the side effects of medications, especially among the elderly of which memory loss and confusion are the most disturbing, limit proper dosing.

In 2003, Dykstra and his colleagues were first to show that injection of botulinum toxin B (Myobloc) into the bladder wall can reduce the urinary frequency and incontinence of patients with OAB (for descriptions of different types of botulinum toxins and their units see Chap. 3). The authors compared the effect of different doses of myobloc starting with 2500, 5000,10,000 and up to 15,000 units which roughly approximate 50 to 250 units of Botox. They found no difference in efficacy between different doses. Subsequently several carefully designed, high quality, double blind studies with Botox in large number of patients confirmed the efficacy of

Botox for management of OAB symptoms. Botox was approved by FDA for treatment of overactive bladder in 2013. The technique of injection is similar to what was described earlier for overactive bladder due to nervous system damage, neurogenic detrusor overactivity (NDO).

Cost Effectiveness

Several studies have shown that despite high cost of Botox therapy, this treatment is cost effective for management of NDO and OAB symptoms. It is used infrequenty, every 6–9 months-has fewer side effects and, in many instances, eliminates the need for taking oral medications. Successful Botox therapy of NDO or OAB leads to reduced number of doctor's office and emergency room visits and less hospitalizations [9].

Prostate and Bladder Dysfunction

Among male patients increased sized of prostate (prostatic hypertrophy) exerts pressure against urethra (the tube draining urine from the bladder) – and causes a variety of symptoms including slowness of voiding, weak urine stream, incomplete emptying and sometimes incontinence. Researchers have tried to show if injection of botulinum toxin into prostate by decreasing the size of prostate can help the urinary problems. The results of research in this area is conflicting. Currently, botulinum toxin therapy (injections) is not recommended for management of urinary symptoms related to enlarged prostate.

Improper Contraction of External Sphincter of the Bladder at the Time of Expected Relaxation

This condition is medically named sphincter-detrusor dyssynergia (SDD) meaning loss of synergy between these two muscles. As was mentioned earlier, when bladder muscle contacts in response the nerve signal, external sphincter muscle (Fig. 8.2) relaxes and lets the urine out of the bladder. In SDD, external sphincter contracts instead of relaxation in response to detrusor contraction. SDD is caused by medical disorders that damage the nerve fibers that control bladder function; these nerve fibers originate from nerve cells of the brain and spinal cord. Disease conditions such as spinal cord trauma, stroke or multiple sclerosis are common cause of DSD. The result of impaired bladder emptying is urine retention, recurrent infections and potential damage to the kidneys.

The technique of injection is well described. Injections can be done by a cystostope which in men is inserted through the penis. After reaching external sphincter, injections are usually performed at 4 points (3, 6, 9 and 12 o'clock locations). Among women, because of the short length of urethra, external sphincter is closer to the surface.

Although many small studies have shown efficacy of Botox in relieving the symptoms of DSD (lasting 3–9 months), better quality and larger studies have not produced convincing results. At the present time, Botox treatment of DDS is not FDA approved but it is performed in some centers off label, by experienced physicians. The main side effect of this treatment is urinary incontinence which results from unwanted degree of weakening of the external sphincter muscle.

Botulinum Toxin Indications in Urogenital Pain Syndromes

As mentioned earlier, injection of US marketed botulinum toxins (Botox, Xeomin, Dysport and Myobloc) into the muscle, not only inhibits the release of acetylcholine in nerve-muscle junction (a neurotransmitter that activates muscle after receiving nerve signal), but also reduces and inhibit the function of a number of pain neurotransmitters. These agents help to convey pain sensation from periphery to the brain. Because of this action, researchers began to explore the effect of botulinum toxin therapy on urogenital pain syndromes. There is now supporting evidence that, at least in three of these conditions, local injection of botulinum toxins alleviates pain. These three conditions consist of male pelvic pain, female pelvic pain and local pain related to chronic bladder infection (interstitial cystitis).

1. Male Pelvic Pain: Male pelvic pain is usually the result of chronic inflammation or infection of prostate (chronic prostatitis). This condition is classified by the National Institute of Health (NIH) as chronic prostatitis/chronic pelvic pain syndrome. It is the most common urological disorder among men under the age of 50 with a prevalence 2.5–16%. The pain is felt in the lower part of the abdomen, pelvis and genitalia and impairs the quality of life by its severity and persistence.

The efficacy of botulinum toxin therapy for male pelvic pain is supported by publication of two high quality studies. Both studies used Botox but the technique of injection was different. In the smaller study which comprised 13 patients, the injection was directed into one of the muscles of the pelvic floor (bulbospongiosus), whereas in the larger study (60 patients), the site of injections was the lateral lobes of prostate (at 3 locations). Both studies used Botox with comparable doses of 100 to 200 units. Investigators of both studies reported that patients described a marked reduction in severity and frequency of pain at 1, 3 and 6 months after injection' concurrent with notable improvements of their quality of life [10, 11]. Using the criteria of the Development Guidelines subcommittee of the American Academy of Neurology (AAN) (see Chap. 3), botulinum toxin therapy for male pelvic pain

would have a level B efficacy (probably effective – one class I study). For this indication, however, Botox does not have FDA approval. The treatment of male pelvic pain with botulinum toxin is hence, off label, based on the currently available supporting literature.

2. Female Pelvic Pain: Chronic pelvic pain among women is most often (71–87%) associated with a medical condition called endometriosis [12]. In endometriosis, a tissue identical to the lining of the uterine cavity (endometrium) is found abnormally in other pelvic organs including the ovaries and the tubes that connect ovaries to uterus. This abnormally located and misplaced issue, increases in size and bleeds just as the normal endometrium does during the menstrual cycle.

The pelvic floor contains a dozen small muscles that surround the rectum and vagina and connect the bony structures of front and back of the pelvis (pubis and tail bones). Abbott and his coworkers from Australia were the first to show that injecting Botox into two of the pelvic floor muscles (one connecting pubis to rectum and one connecting pubis to tailbone) relieves pelvic pain in a group of women, a majority of whom had endometriosis. Their study consisted of sixty women, 30 of whom received 80 units of Botox and 30 received placebo (normal saline) [13]. The patients were followed at 4-week intervals for 26 weeks. In addition to relief of pelvic pain, women who received Botox, reported having less pain during intercourse (dyspareunia) compared to those who received saline. Dr.Abbott and his colleagues observation, was supported by several other observations, among them a recent study that reported pain relief and improvement of quality of life following Botox injection in women with pelvic pain who were followed 6 months [14]. Close to 5% of the patients reported transient urinary and fecal incontinence as side effects of Botox injections. Currently, Dr.Barbara Karp and her colleagues at the National Institutes of Health are investigating the effects of botulinum toxin injections in women with pelvic pain and endometriosis. The preliminary results of this carefully crafted study are encouraging; the full results will be available, hopefully, over the next few months.

3. Pain related to chronic bladder infection (interstitial cystitis, bladder pain syndrome): Bladder pain syndrome is a debilitating condition that affects millions of people worldwide. It is believed to be due to chronic inflammation of the internal bladder lining (in contact with urine) that leads to irritation, pain in the area of the bladder, urinary frequency and urinary urgency. Failure of body's immune system is suspected in some patients but the cause of this bladder problem is generally unknown. No effective treatment is currently available. Instillation of hyaluronic acid into bladder helps some patients and reduces the irritation of the bladder lining, but the results are often temporary and pain recurrence is common. Pain killers offer only modest pain relief in bladder pain syndrome. In recent years, several, carefully designed studies have shown that injection of bladder wall with botulinum toxins can relieve pain and other symptoms of bladder pain syndrome. The most recent of these high- quality studies, found that both injection of the body of bladder and bladder trigone relieved bladder pain in

about 50% of the patients, a considerably higher rate of success compared to that achieved by the placebo (saline) injection [15]. Although Botox injections of the bladder are not yet approved by FDA for treatment of bladder pain syndrome, the American Urological Association recommends it as the fourth mode of treatment for this indication based on the currently available literature.

Conclusion

Botulinum toxin injection into bladder wall improves symptoms related to bladder dysfunction and discomfort (urgency, frequency). Botulinum toxin therapy is approved by FDA for treatment of bladder overactivity either related to nerve damage (neurogenic detrusor overactivity-NDO) or bladder overactivity of undetermined cause (overactive bladder-OAB). FDA has not approved botulinum toxin therapy for other bladder disorders, but the existing literature supports its efficacy in male and female pelvic pain syndrome and in pain related to chronic bladder inflammation (bladder pain syndrome). Other potential areas of botulinum toxin treatment utility in the field of bladder dysfunction or pelvic pain such as pelvic pain related to enlarged prostate, bladder dysfunction due to lack of synergy between bladder's detrusor muscle bladder and bladder's sphincter are also being currently explored.

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