Chapter 10
Botulinum Toxin Treatment of Bladder and Pelvic Disorders

Abstract Botulinum toxins blocks the release of neurotransmitters at nerve-muscle junction. Neurotransmitters are chemicals that convey the 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 30 years have proved the efficacy of botulinum toxin injection into the bladder wall in improving bladder overactivity problems. The symptoms of bladder dysfunction, overactivity, urinary urgency and incontinence impairs the patients' quality of life. Botulinum toxins are also effective in relieving pelvic pain in both genders due to their blocking effect on pain neurotransmitters (substance P, glutamate and CGRP).

Keywords Botulinum toxin · Botulinum neurotoxin · Bladder overactivity · Urinary urgency · Incontinence of urine · Pelvic pain

Introduction

Bladder functions through the action of its muscles and nerves. 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 secreted at the nerve endings and their role is activating 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 25 years have proven the efficacy of botulinum toxin injection into the bladder wall in improving bladder overactivity problems. The bladder overactivity problems are either due to damage to the bladder nerves seen in spinal cord injury and 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 conditions of unknown cause are simply

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designated as 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 therapeutic agent when prepared in an injectable and safe form is presented in detail in Chap. 1. There are eight serological types of the toxin (A to G and X). Different types of type A and type B toxin are described in detail in Chap. 3.

Because of the powerful effect of botulinum toxins on nerve- muscle junction (see Chap. 2 for details), over the past 30 years, botulinum toxins have become first line drugs 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, 2]. In addition, through the same mode of action (blocking the release of acetylcholine release at nerve-muscle junction), botulinum toxins' role has now been established as a major mode of treatment for improving and reducing increased muscle tone and muscle spasm (spasticity) which occur after stroke or after brain or spinal cord injury [3–5].

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

Physiology of Bladder Function and the Role of Detrusor Muscle

In healthy subjects, human kidneys generate 800–2000 milliliters of urine per 24 h. The urine that is generated by the kidneys is carried to the bladder by two tubes called ureters (Fig. 10.1).

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 urine to the outside from the trigone is through a hole that opens

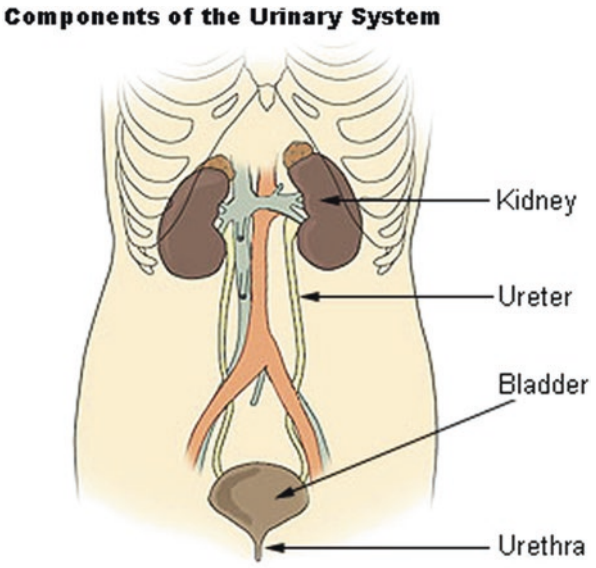

Fig. 10.1 Kidney's, ureters, bladder and urethra. (Courtesy of Wikibooks. Licensed under https://creativecommons.org/licenses/by-sa/4.0/)

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. 10.1). Storage and emptying of the urine are managed by three essential muscles:

1. Detrusor muscle (Fig. 10.2): This is the main muscle of the bladder wall which, while relaxed, allows the bladder to expand and store urine; the contraction of this muscle is essential for the drainage of urine.
2. Internal urethral sphincter (Fig. 10.2): 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 urethral sphincter (Fig. 10.2): This muscle 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 bladder muscles to relax resulting in release and drainage of urine. The detrusor muscle

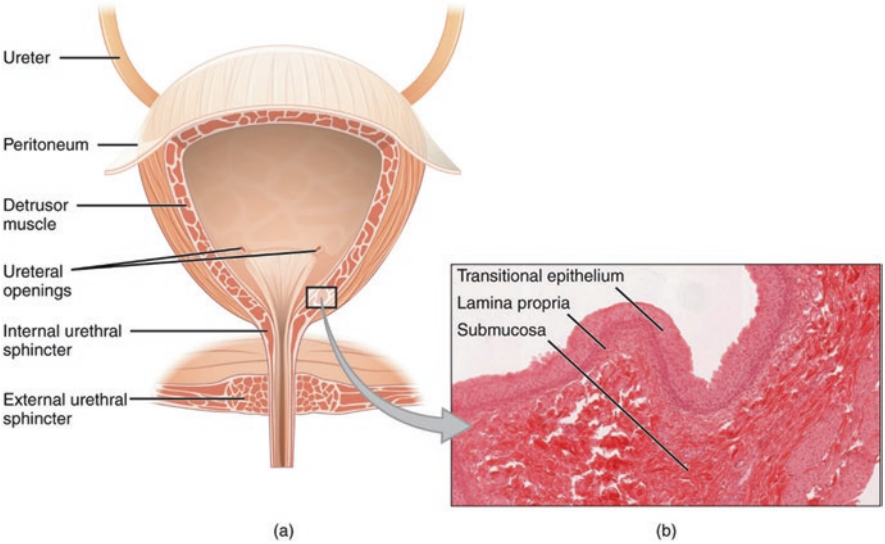

Fig. 10.2 Bladder: Base (at the top), trigone, detrusor muscle, internal and external sphincters. (Courtesy of https://upload.wikimedia.org/wikipedia/commons/d/dc/2605_The_Bladder.jpg)

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 resulting in passage of the urine from bladder to urethra for micturition. 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 some 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 (neurogenic bladder- NB) is the most common type of bladder dysfunction in multiple sclerosis (MS) and spinal cord injury (SCI). Research and clinical observation have shown that 50–90% and 70–84% of the patients with MS and SCI develop NB, respectively, sometimes during the course of their illness [6–8]. In both MS and SCI, presence of NB significantly impairs the patient's quality of life due to urinary urgency and incontinence.

Control of bladder function takes place at several levels in the central nervous system that involves the 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 partial spinal cord injury damage the nerve cells and nerve fibers that control bladder function. The result of this damage is increased excitability of the nerve fibers that descend from the brain to the bladder and provide nerve supply to the detrusor muscle of bladder. This is similar to what happens to other muscles of the body in case of central nervous system damage; the affected muscles became overactive. The term reflex bladder is also used sometimes for NB characterizing the overactivity of the bladder's detrusor muscle in NDO/NB.

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 retention of some 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 as trying to delay voiding upon the urge to urinate. Patients start with 5–10 min micturition delay, gradually extends the delay 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 an 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. 10.3). 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 seeing satisfactory results with this exercise.

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 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 (anticholinergics) 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. Mirabegron, a newer drug for preventing urinary incontinence does not cause dryness of the mouth and constipation. Unfortunately, long-term effects of medications in treatment of

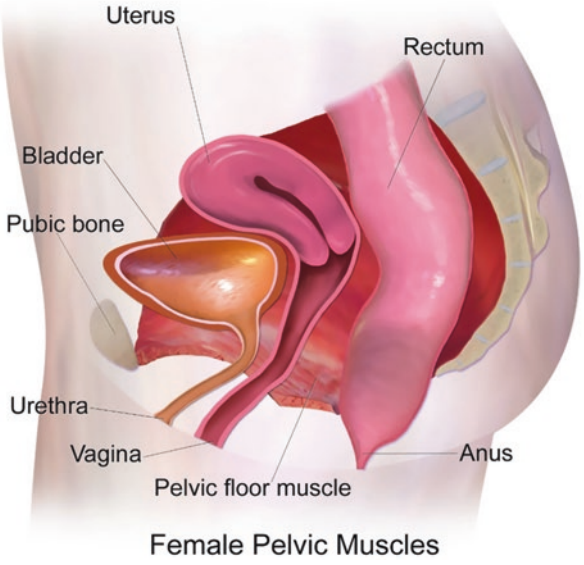

Fig. 10.3 Position of the bladder and pelvic floor muscles- Courtesy of Wikimedia. (Reproduced under Creative Commons Attribution Share-Alike license (CC-BY-SA))

overactive bladder related to nerve damage is disappointing. Research has 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 [8].

Botulinum Toxin Treatment of Neurogenic Detrusor Overactivity (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 patient being 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 that 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 [9–11]. 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 in both adults and children have demonstrated maintenance of efficacy after repeated injections of Botox over years (3–6 years) with the time interval between injections varying from 6 to 11 months [12–14].

During the past 5 years, high quality studies (double-blind, placebo-controlled) have explored the efficacy of other type A botulinum toxins in treatment of neurogenic bladder. In one study of 47 patients with NB/NDO, investigators found the injections of 750 units of Dysport (each unit of Disport approximates 2.5 units of Botox) improved patients' urinary incontinence significantly [15]. This positive response of NB to Dysport was duplicated later in a larger, high quality study that included nearly 500 patients [16]. In this study, reduction of urinary incontinence correlated with significant improvement of patients' quality of life. In a recent study [15], investigators compared the results of Botox injection into the bladder with bladder injection of Xeomin (another type A toxin with comparable units to Botox) in 57 patients with neurogenic bladder secondary to spinal cord injury or multiple sclerosis. Patients received a total dose of 200 units distributed over 30 sites. Patients were followed for 12 weeks. Both botulinum toxins were equally effective in reducing urinary urgency, incontinence and improvement of patient's quality of life. The side effect profile was also similar for the two toxins. In 2021, FDA approved Botox injections in children over 5 years of age for neurogenic bladder leading to incontinence based on publication of high quality studies [12, 17].

The main side effect of Botox treatment of neurogenic detrusor overactivity/neurogenic bladder is urinary retention. In a study of over 500 patients with NB secondary to MS or SCI,, authors noted urinary retention following Botox injection into the bladder in 29.5% and 7.2% patients with MS and SCI, respectively [18]. When this complication occurs, patients need to do self-catheterization for removing trapped urine from the bladder. For many patients with severe spinal cord injury or advanced multiple sclerosis, this may not be a major issue since they are already doing self-catheterization. The need for self-catheterization after Botox injections, however, decreases with the passage of time. In one study of 227 patients with NDO, researchers have shown that the need for self-catheterization in the third and fourth year after initiation of Botox therapy dropped to 8% and 0% respectively [14]. Increased urinary tract infections (reported in approximately half of the treated patients [18]) and bleeding (usually mild) into the bladder are other complications that require close attention and monitoring.

Injection Technique

Prior to bladder injections, the bladder wall is numbed with an anesthetic via an endoscope. Endoscope is a device that allows to explore and visualize the bladder wall while simultaneously allowing injection into the bladder muscle.

Prior to botulinum toxin injection, injection of an anesthetic, such as lidocaine or alkalinized lidocaine is recommended to numb the bladder wall [19, 20]. For Botox

injections, one group of experienced injectors recommends diluting 100 units of Botox in 10 cc of normal saline [21]. 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 (lower part of bladder, Fig. 10.3) and recommends a total dose of 200 units of Botox. As described earlier, recently published high quality studies indicate that Xeomin and Dysport (two other type A botulinum toxins) may be equally effective as Botox for treatment of urge incontinence in NB.

Currently, there is a debate on the optimum number of injection sites. While some authors advocate 20–30 injection sites, others have found that injecting the toxin into 15 sites may be sufficient.

In recent years, several authors have recommend including the trigone of the bladder in the injected plan since this region of bladder is rich in nerve fibers. 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 9–10 injection sites with a total Botox dose of 100 units (Fig. 10.4). For patients with severe symptoms who are already catheterizing themselves, 30–40 injection sites are recommended with a total Botox dose of 200 units.

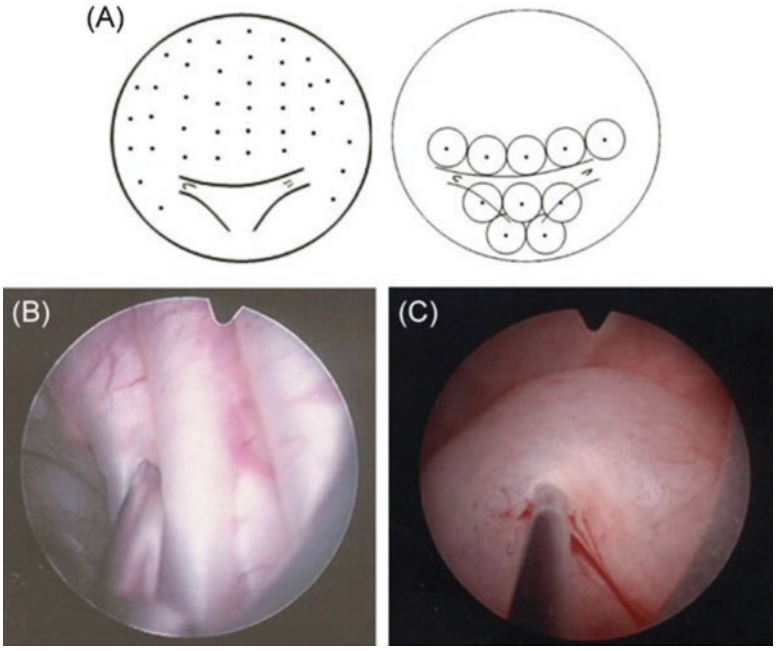

Fig. 10.4 Technique of bladder injection: (**a**) (top left) 30 injections for patients with severe symptoms. (**a**) (top right) 10 injections for patients with mild symptoms. From Dasilva and coworkers. Toxicon 2015. (Reproduced with permission from the publisher Elsevier. (**b** and **c**) site of injection just under the mucosa of bladder surface)

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 75 years of age or older [22]. 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, anticholinergic medication, and more recently introduced drugs such as mirabegron and oxybutyrin. As mentioned earlier side effects of these drugs and lack of sustained action is a reason for exploring new modes of treatment.

In 2003, Dykstra and his colleagues were first to show that injection of botulinum toxin B) 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) [23]. The authors compared the effect of different doses of myobloc starting with 2500, 5000, 10,000 and rarely up to 15,000 units; the first three roughly approximate 50–100 and 200 units of Botox, respectively. 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 [24–26]. Based on these studies, Botox was approved by FDA for treatment of overactive bladder in 2013. The technique of Botox injection into bladder is similar to what was described earlier for management of urinary incontinence in neurogenic detrusor overactivity (NDO)/ neurogenic bladder (NB).

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 infrequently, 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 [27].

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 (detrusor) contracts in response the nerve signal, external sphincter muscle (Fig. 10.2) relaxes and lets urine out of the bladder. In SDD, external sphincter

undergoes contraction 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 causes of DSD. The result of impaired bladder emptying is urine retention, recurrent infections and potential damage to the kidneys due to back up of the urine.

Technique of Toxin Injection in DSD Injections can be done by a cystoscope 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). In women, because of the short length of urethra, external sphincter is closer to the surface.

Several studies have shown efficacy of Botox in relieving the symptoms of DSD (lasting 3–9 months) [28–32]. At 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 (a neurotransmitter that activates muscle but also reduces and inhibits 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).

Male Pelvic Pain

Male Pelvic Pain 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 of 2.5–16% [33]. The pain is felt in the lower part of the abdomen, pelvis and genitalia and impairs the quality of life due to 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 100–200 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 [34, 35]. Using the criteria of the Development and 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 based on I and one class II). For this indication, however, Botox does not have FDA approval yet. The treatment of male pelvic pain with botulinum toxin is, hence, currently off label based on the supporting literature.

Female Pelvic Pain Chronic pelvic pain in women is most often (71–87%) associates with a medical condition called endometriosis [36]. In endometriosis, a tissue identical to the lining of the uterine cavity (endometrium) is found abnormally in other pelvic organs including the ovaries, the tubes that connect ovaries to uterus and in the peritoneum. 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 tailbones). Dr. 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 60 women, 30 of whom received 80 units of Botox and 30 received placebo (normal saline) [37]. The patients were followed at 4-week intervals for 26 weeks. In addition to relief from 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 study that reported pain relief and improvement of quality of life following Botox injection in women with pelvic pain [38]. Close to 5% of the patients reported transient urinary and fecal incontinence as side effects of Botox injections. In another study that combined injection of Botox into pelvic floor muscles with pelvic floor physiotherapy, 58% of the affected women reported improvement of their pelvic pain [39]. Dr. Barbara Karp and her colleagues at the National Institutes of Health investigated the effects of botulinum toxin injections in women with pelvic pain and endometriosis in a double-blind, placebo-controlled, carefully crafted protocol. The preliminary results of this protocol are encouraging; the full results will be available, hopefully, in the near future. In a recent review of literature on this subject, Dr. Karp has emphasized the need for more high quality studies in this area [40].

Pain Related to Bladder Infection (Interstitial Cystitis/Bladder Pain Syndrome) Bladder pain syndrome (BPS) or interstitial cystitis (IC) is a debilitating condition that affects millions of people worldwide. It is believed to be due to chronic inflammation of the internal bladder lining (part 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 currently 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. Hydrodistention (distending the bladder with water) also produces some degree of pain relief in some patients. The effects of painkillers in interstitial cystitis (IC) is often not sustained.

In recent years, several studies have shown that injection of bladder wall with botulinum toxins can relieve pain and improve quality of life in patients with interstitial cystitis/bladder pain syndrome [41–45]. This is probably via the dual action of botulinum toxin: 1- relaxing the bladder wall and 2- blocking the effect of chemicals known as pain transmitters (described earlier in this chapter and in detail in Chap. 3). Preference for injection locations varies among different investigators. Some prefer to inject the body of bladder and others have found injecting into bladder trigone which is rich in nerve fibers (usually 10 injection sites) more helpful [45–47].

One comparable study has shown no difference between the two locations (trigone versus body of the bladder) [48]. The recommended dose for Botox is 100 units and for Dysport (another type A toxin) 300 units [48]. In one study, combining Botox injection with hydrodistention was more effective in relieving the symptoms of IC than hydrodistention alone [49]. Repeated injections of Botox for treatment of IC have been found to be generally safe [50] with sustained long-term efficacy (over years) achievable [51].

Botulinum Toxin Therapy for Enlarged Prostate

Among male patients, increased size of the 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 have ben conflicting. Currently, botulinum toxin therapy (injections) is not recommended for management of urinary symptoms solely related to enlarged prostate.

Conclusion

Many drugs have been tested for treatment of urinary urgency or incontinence resulting from neurogenic bladder [NP] or overactive bladder [OAB], but the results have often been disappointing due to poor sustained efficacy and disturbing side

effects [52]. 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 bladder/neurogenic detrusor overactivity-NB/NDO) or bladder overactivity of undetermined cause (overactive bladder-OAB). FDA has not yet approved botulinum toxin therapy for treatment of interstitial cystitis (bladder pain syndrome), but the American Urological Association advocates it as one mode of therapy for this painful condition. Botulinum toxin therapy (injections) is probably effective in relieving male pelvic pain (level B evidence- see Chap. 3). For female pelvic pain the preliminary data are encouraging, but experts encourage waiting for the results of more high quality studies.

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