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Role of Onabotulinum Toxin-A Injection in the Management of Pain and Sexual Dysfunction in Women with BPS/IC

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Abstract

Purpose of Review In this review, we aimed to summarize the effects of BoNT-A injections on pain and sexual dysfunction in women with BPS/IC in the light of current literature.

Recent Findings In recent years, randomized controlled studies have provided evidence for the positive effects of intravesical BoNT-A treatment on pain and quality of life scores in patients with BPS/IC. Trigonal injections have demonstrated similar efficacy and safety to those administered to the bladder body. Furthermore, noninvasive alternatives such as low-energy shock wave plus intravesical instillation, hydrogel-based instillation, and liposome-encapsulated BoNT-A instillations have been explored for patients with BPS/IC. The studies examining the impact of BoNT-A on sexual functions are limited. Only one published study has shown improvement in sexual functions with intravesical BoNT-A.

Summary Intravesical BoNT-A treatment in BPS/IC patients is an effective and safe method recommended by the guidelines. In the light of current literature, this treatment also provides an improvement in sexual functions.

Keywords Bladder Pain Syndrome · Interstitial Cystitis · Onabotulinum Toxin-A · Bladder Pain · Sexual Dysfunction · Women

Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is one of the chronic pelvic pain syndrome that is not commonly encountered but significantly impairs the quality of life. Epidemiological studies have yielded a wide range of results due to the controversial diagnosis of BPS/IC over the years and the lack of standardized evaluation methods. In this context, prevalence rates ranging between 0.06 and 30% have been reported in the recent European Association of Urology (EAU) guidelines [1]. The American Urological Association (AUA) defines BPS/IC as "a reported unpleasant feeling (discomfort, pressure, pain) related to the bladder, accompanied by persistent lower urinary tract symptoms for more than six weeks in the absence of infection or other recognizable cause" [2]. As implied by the terminology, chronic pain constitutes the primary symptom of IC/BPS. Since the etiology and pathophysiology of IC/BPS remain poorly understood, there is no definitive curative therapy. Consequently, most treatment methods primarily aim to alleviate pain [3]. However, pain is not the sole symptom in these patients. Although "sexual dysfunction" is not included in the definition of IC/BPS, similar to pain or lower urinary tract symptoms, it is a crucial symptom negatively affecting the quality of life. Sexual dysfunction is highly prevalent among this patient population [4].

There are various treatment options used for BPS/IC; however, there is no method to fully cure the disease. The primary aim of treatment is to improve symptoms, enhance the quality of life, and minimize treatment-related adverse events. Onabotulinum toxin-A (BoNT-A) is one of the treatments with proven efficacy in BPS/IC [5]. This review will summarize the effects of BoNT-A injections used in the treatment of BPS/IC patients on pain and sexual dysfunction, based on the current literature.

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Etiopathogenesis of BPS/IC, Characteristics of Pain, and Sexual Dysfunction

Despite extensive research, the etiology of BPS/IC remains incompletely understood. Neurogenic inflammation, mast cell activation, urothelial dysfunction, C-fiber neuroplasticity, and neural upregulation are some of the hypotheses implicated in the etiology of BPS/IC.

While chronic pain and discomfort during bladder filling are the primary complaints in these patients, IC/BPS has also been conclusively associated with significant sexual health issues that can adversely impact the quality of life [6]. Women with IC/BPS have a considerably higher prevalence of sexual dysfunction (SD) compared to the general population. In a study by Bogart et al., 88% of the women with IC/BPS reported having SD [4]. Other recent study demonstrated that Asian BPS/IC patients, compared with an asymptomatic control group, experienced more sexual dysfunction, worse vaginal health, and more vulvodynia [7]. Although pain during sexual activity is the most commonly reported sexual dysfunction symptom in women with BPS/IC, other symptoms, such as a decrease in desire and lubrication, as well as a decrease in orgasm frequency, have also been reported in this patient group compared to the general population [4, 8, 9]. Dyspareunia may result from direct pressure on the bladder or irritation of the urethra during sexual intercourse. Treating pain in the bladder and urethra in these patients can also contribute to the improvement of sexual function. Furthermore, both the bladder and vaginal vestibule develop from the endoderm and genitourinary sinus. Consequently, dyspareunia-associated vulvodynia is the most common form of superficial genital pain, affecting 48% of patients with BPS/IC [10]. It causes erythema, tenderness on examination, and typical pain with penetration, localized to the vaginal entrance. Additionally, afferent C-fiber activation from the bladder and vulva leads to hyperalgesia and sensory changes in the normal dorsal horn, initiating a pain cycle [8]. Pelvic floor muscle dysfunction is another important cause of dyspareunia. Vaginismus may also be seen as a result of muscle contractions triggered by pelvic floor muscle dysfunction. Even the fear of experiencing dyspareunia during sexual activity can lead to more contracted pelvic floor muscles, exacerbating the pain. Taken together, a combination of interrelated factors is believed to contribute to sexual dysfunction in BPS/IC patients.

Effect of BoNT-A on Pain in BPS/IC Patients

The use of botulinum toxin A (BoNT-A) in the treatment of lower urinary tract symptoms began in the late 1980s. Initially, it was used to treat detrusor sphincter dyssynergia in patients with spinal cord injury [11]. Later, it was applied to treat neurogenic detrusor overactivity in patients with spinal cord injury [12]. Subsequently, it proved successful in idiopathic detrusor overactivity and overactive bladder patients [13]. In 2004, Smith et al. applied BoNT-A to 13 patients with IC. They demonstrated that BoNT-A improved both symptomatic and functional outcomes by providing an antinociceptive effect on bladder afferent pathways in patients with IC [14]. BoNT-A intravesical injection has been proven effective for the management of IC/BPS. A recent meta-analysis found BoNT-A treatment to be the most effective among BPS/IC treatments based on changes in global response assessment [15]. Several studies have supported this finding, leading to the recommendation of this treatment method in the EAU and AUA guidelines [1, 2].

Botulinum toxin is a neurotoxin known for centuries. Since it was found to be a toxin generated by the bacterium *Clostridium botulinum*, BoNT has been widely used to treat neuropathic pain syndromes and dystonic diseases [16, 17]. It generates partial paralysis and atrophy by reversibly chemically denervating the muscle fiber and blocking the release of acetylcholine at the neuromuscular junction [18].

Apart from acetylcholine, nitric oxide, adenosine triphosphate, substance P, and the calcitonin gene-related peptide are among the neurotransmitters and neuropeptides that botulinum toxin can inhibit [19, 20]. In this way, BoNT-A exerts anti-inflammatory effects and inhibits local inflammation. Additionally, in cases of bladder inflammation, it may suppress the production of transient receptor potential vanilloid subfamily-1 (TRPV1) and purinergic receptor P2X3-IR [21]. Intravesical BoNT-A injections can thus decrease both bladder pain and bladder sensation. Some authors hypothesize that BoNT-A can reduce chronic pain by affecting peripheral nociceptive neurons and generating central desensitization by transporting toxins backward into the central nervous system [22]. However, current research indicates that additional mechanisms, such as anti-inflammatory activities, sensory regulation in the urothelium, and inhibition of detrusor muscle activity, may be involved in the potential processes of using BoNT-A for the treatment of IC/BPS [23]. Abnormal high tension or contraction of smooth muscle has been suggested as a potential mechanism for the development of chronic visceral organ pain [24]. It has been suggested that pain can originate in the bladder in this way and that this tension can be alleviated with BoNT-A treatment, providing pain relief [25]. Another hypothesis is that in patients treated with BoNT-A, sensory nerve functions are modulated, resulting in both pain reduction and reduction in urgency in patients with IC/BPS or overactive bladder

[26]. Based on animal experiments and in vitro studies, it is believed that BoNT-A treatment provides an anti-inflammatory effect by changing anti-inflammatory cells and mediators in the urothelium, improving the urothelial barrier function, and making a positive contribution to BPS/IC treatment [25].

The bladder dome and trigone have different innervations, and this regional difference can guide the anatomical treatment target. Basic research suggests that the trigone and bladder floor are surrounded by small unmyelinated afferent nociceptive C-fibers that are upregulated in BPS/IC [27]. These C-fibers are likely responsible for transmitting the sensation of pain and urgency but do not appear to have any role in normal bladder function. The remainder of the bladder is surrounded by A-delta (afferent) and parasympathetic (efferent) nerves, which allows the recognition of bladder fullness and detrusor contraction, respectively [28]. Treatment modalities should ideally target the pathophysiology while preserving normal physiology. Although selective targeting of upregulated C-fibers in the trigone in the bladder suggests that it will be effective, especially in the relief of pain and urgency, the current studies do not fully support this hypothesis. Recent studies by Jiang et al. and Evans et al. showed that BoNT-A injections to the trigone in patients with BPS/IC have similar efficacy with trigone-sparing injections [29••, 30••]. Only trigonal injections of BoNT-A are also effective at reducing pain, as demonstrated by Pinto et al. in a randomized placebo-controlled trial [31••].

Although intravesical injections of BoNT-A are efficacious for functional bladder abnormalities, they are invasive and uncomfortable due to adverse effects such as bladder pain and UTIs. Recently, novel delivery methods have been tried to administer BoNT-A without injection, making the procedure less invasive and minimizing adverse effects. According to laboratory research, liposomes are able to transport BoNT-A across the uroepithelium and affect sub-urothelial nerve endings [32]. In a randomized controlled trial in BPS/IC patients, intravesical administration of liposome-encapsulated BoNT-A 200U was compared with BoNT-A 200U with normal saline and normal saline alone [33]. Although bladder pain improved in the liposome-encapsulated BoNT-A group, similar improvement was observed in the other two groups. Liposome-encapsulated BoNT-A failed to show any significant benefit compared to BoNT-A or placebo with normal saline, possibly due to a significant placebo effect [33].

Another promising new application is the instillation of TC-3 hydrogel and BoNT-A. Rappaport et al. conducted a single-arm study to treat BPS/IC patients with intravesical administration of TC-3 hydrogel-embedded 200 Units of BoNT-A [34]. Hydrogels are hydrophilic polymers that are extremely absorbent, and they can hold water while preserving their structure [35]. Hydrogels enable drugs to be encapsulated and create a setting resembling animal tissues. They have been used as effective drug delivery systems. Bladder pain and urinary frequency were significantly reduced at the 12-week follow-up with the instillation of TC-3 hydrogel-embedded BoNT-A in this single-arm study [34]. This study was promising; however, its efficacy needs to be proven with placebo-controlled studies involving a sufficient patient population.

Low-energy shock wave (LESW) plus intravesical instillation of BoNT-A was also studied for BPS/IC patients [36]. Jiang et al. conducted a pilot clinical study of a case series using suprapubic LESW to supplement intravesical BoNT-A delivery. Authors performed intravesical instillation of 200 U BoNT-A, and then LESW treatment was applied. Based on the findings, LESW was able to transfer BoNT-A through the bladder urothelium and modulate its effects on bladder nerve endings. Although the clinical effectiveness in the initial study was not particularly impressive, it is reasonable and optimistic to utilize LESW to assist intravesical BoNT-A administration without the need for injection [36].

Effect of BoNT-A on Sexual Dysfunction in BPS/IC Patients

In a recently published systematic review, the effect of BPS/IC treatment on sexual function was investigated. In this study, only ten studies published before 2020 met the study inclusion criteria and were included in the review. However, onabotulinum toxin-A injection was not evaluated in any of these studies [37••]**.** Until 2023, there was no study in the literature investigating the effect of BoNT-A treatment on sexual function in BPS/IC patients. Then, the first study investigating the effect of BoNT-A injection on sexual function in female patients with BPS/IC was published. The authors showed that there was a statistically significant improvement in Female Sexual Function Index (FSFI) scores with BoNT-A injection treatment. This significance also continued in all FSFI subdomains. In addition, the authors observed a statistically significant improvement in the Interstitial Cystitis Symptom and Problem Index of the O'Leary-Sant Questionnaire and Visual Analog Scale (VAS) scores in the study group [38••].

However, there are no experimental or clinical studies investigating the mechanism of action of BTX-A in improving sexual functions in BPS/IC. We know that studies investigating the effect of BoNT-A on sexual functions are insufficient. As such, there are no experimental or clinical studies investigating the mechanism of action of BTX-A in the improvement of sexual functions. We believe that when pain scores decrease, the pain experienced during sexual activity diminishes, leading to an improvement in sexual functions.

On the other hand, BoNT-A treatment is also used in the treatment of overactive bladder, and studies investigating the effect of Botox on sexual functions have been conducted in this patient group. In a study, a statistically significant increase was found in the total FSFI score of 32 patients diagnosed with overactive bladder (OAB) after treatment with 100 U onabotulinum toxin-A. In the subgroups, significant improvement was found with BTX-A in all domains except desire and pain [39]. In a recent systematic review, it was reported that there was a statistically significant increase in the total FSFI score and in all subgroups except pain in patients who underwent 100 U BTX-A with the diagnosis of OAB [40]. Although we are talking about two diseases with different pathogenesis, these results suggest that BoNT-A therapy can improve sexual functions completely independent of pain. In conclusion, we think that complex mechanisms intertwined in disease pathogenesis may be similar in treatment efficacy. As a result, we believe that treatment effectiveness may be more complicated, just like pathogenesis.

Conclusion

Intravesical BoNT-A treatment in BPS/IC patients is an effective and safe method recommended by the guidelines. In the light of current literature, this treatment also provides an improvement in secular functions. However, randomized controlled studies with larger samples are needed to prove the positive effects of BoNT-A treatment on sexual functions.

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Declarations

Competing interests The authors declare no competing interests.

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- • Of importance
- •• Of major importance

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