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Original Article

Evaluation of several botulinum toxins-A delivering systems into the bladder in interstitial cystitis/painful bladder syndrome (IC/PBS)

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Abstract: Botulinum toxins were primary suggested for the neurogenic lower urinary tract dysfunction (LUTD) treatment about thirty years ago. The application of BTX-A in LUTD have just developed and the approval of BTX-A injection confirmed in for patients with both overactive bladders (OAB) and neurogenic detrusor overactivity (NDO). Actually the BTX-A medication in interstitial cystitis/bladder pain syndrome (IC/BPS) is not licensed, but there is under consideration. Despite BTX-A is recommended to treat patients with interstitial cystitis/bladder pain syndrome (ICBPS) under different occasions, its efficacy and safety in the cure of (IC/BPS) is under consideration. One difficulty is related to the toxin delivering systems. It is shown that there is no difference in BTX-A injection to body or trigone but there is a need on further large-scale studies over this subject. Moreover, Hydro distention can boost the therapeutic effect of BTX-A for IC/BPS patients. Additional studies should consider the safety and efficacy of BTX-A injection in the treatment of BTX-A.

Keywords: Interstitial cystitis/bladder pain syndrome (IC/BPS), botulinum toxin-A, delivering systems

Introduction

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic disease with a series of bladder symptoms, including urinary frequency, urgency, increased nocturia, and bladder and pelvic pain [1, 2] that last more than 6 weeks in the absence of infection or other identifiable causes [3]. The pathogenesis of IC/BPS remains unclear, with different hypotheses proposed, such as dysfunction of extracellular matrix of the glycosaminogly can (GAG) layer, down regulation of tight junction proteins, increased urothelial permeability, mast cell activation, neurogenic inflammation, and C-afferent fiber neuroplasticity or even CNS sensitization [2-6]. The incidence of IC/PBS is variable. The prevalence of IC/PBS in United States is about 60-70 cases per 100,000 women [7] whereas 18 cases per 100,000 women in Europe and 3-4 cases per 100,000 women in Japan [8] with global female to male ratio of 45:8 [6]. Studies also demonstrated that IC/PBS morbidity is related to race, age, and gender, moreover it is most likely to affect women with age of 30 to 50 [9].

Although the American Urological Association (AUA) proposed self-care and oral agents such as Amitriptyline, cimetidine, hydroxyzine or pentosane polysulfate as the first and second lines of treatment of IC/PBS while intradetrusor botulinum toxin-A (BTX-A) is designated as the fourth line [10] but there is still a debate about the effect of BTX-A and the way it is administrated in treatment of this disease.

In this review we discuss the available mechanisms and efficacy of different methods of delivering BTX-A into the bladder for treatment of BPS/IC.

BTX-A structure and functions

Botulinum toxin (BTX) is a neurotoxin protein produced by the bacterium Clostridium botulinum and are types A-F, and G with the ability of inhibition the acetylcholine secretion at neuromuscular junction [11]. Infection with the bacte-

rium is the lethal disease botulism but its toxin is used in medicine and cosmetics as well.

BTX-B inhibits acetylcholine release at the neuromuscular junction through a three stage procedure: 1) Heavy Chain mediated neurospecific binding of the toxin, 2) internalization of the toxin by receptor-mediated endocytosis, and 3) ATP and pH dependent translocation of the Light Chain to the neuronal cytosol where it acts as a zinc-dependent endoprotease cleaving polypeptides necessary for neurotransmitter discharge. BTX-B binds to and cleaves the synaptic Vesicle Associated Membrane Protein (VAMP or synaptobrevin) which is a factor of the protein complex in charge of docking and fusion of the synaptic vesicle to the presynaptic membrane, a necessary step to neurotransmitter release.

The etiology and pathophysiology of IC/BPS are not completely known yet, however there is increasing evidence that neurogenic inflammation activates bladder afferent nerves and triggers bladder pain and bladder overactivity [12]. As the mechanism of action of BTX-A involves inhibition of suburothelial neurotransmitter release of sensory neuropeptides and neurotransmitters that regulates pain and inflammation [13, 14], there is a rationale for its use in IC/BPS.

Several studies carried out in the recent years to show and validate the effect of botulinum toxin A (BTX-A) in treatment of IC/BPS. In most studies IC/BPS symptoms were usually assessed by using a female modification of the chronic prostatitis syndrome index (CPSI-F) and the O'Leary-Sant questionnaire score (OLS), that includes the interstitial cystitis symptoms index (ICSI), and interstitial cystitis problem index (ICPI). Self-patient assessment usually was performed using a 10 point visual analogue scale (VAS). A voiding diary and an urodynamic study were also included in some evaluations.

Clinical trials over BTX-A

The very first studies on effect of botulinum toxin A (BTX-A) almost use the method in which botulinum neurotoxin-A (BoNT-A) is injected to the base and trigone of bladder [15] which is still being used in most of studies carried out in this topic. Its crystal 3D structure of BTX-A is resented in **Figure 1**.

Since various animal studies on anatomical dispersion of bladder afferents nerves showed that most nociceptive bladder afferents are located in trigone [16, 17], some recent studies try to focus their botulinum injections specifically to trigone area. Recently, in 2018 Almeida Pinto et al. prefaced a pilot, single center, randomized, double blind and placebo-controlled trial, to compare the efficacy and safety of trigonal injections of Onabotulinumtoxin A and saline in patients with BPS/IC. The research was carried out on 19 women with more than 6 months' history of BPS/IC and pain for longer than 4 months. Trigonal injection of Onabotulinumtoxin A 100 U in 10 cases and saline as placebo in 9, was administered 10 times of 1 ml. After 12 weeks, Onabotulinumtoxin A had significantly reduced pain when comparing with placebo (-3.8 ± 2.5 vs. -1.6 ± 2.1, $P < 0.05$). 60% of the patients undergone for onabotulinumtoxin A treatment and 22% of those treated with placebo achieved a 50% or greater reduction in the pain VAS. OnabotulinumtoxinA significantly improved O'Leary-Sant scores and quality of life over placebo at weeks 4, 8 and 12. In addition, OnabotulinumtoxinA effectively improved quality of life more than saline at weeks 4, 8 and 12, and it was tolerated well [18]. Another prospective, randomized, double-blinded clinical trial, carried out by JF Jhang and HC Kuo in 2018 tried to compare the effectiveness of botulinum toxin-A injections to trigone vs. body. They investigated the clinical effectiveness of BoNT-A intravesical injection on 39 patients which are divided into two groups in which 20 patients received 20 injections in body and the other group of 19 patients got 10 injections in trigone. VAS score has decreased for more than 2 points in 65.0% of patients of bladder body group vs. 52.6% of patients in trigone group ($P = 0.43$). 9 (45%) patients with bladder body injection and 10 (52.6%) patients with trigonal injection experience a symptom improvement more than 2 GRA score ($P = 0.63$). Nine (45.0%) patients in bladder body group and 10 (52.6%) in trigonal group experienced dysuria as treatment's negative effect ($P = 0.52$). Urodynamic evaluations showed that the cystometric bladder capacity and voided volume did not increase in either group, but Qmax was significantly increased only in the trigone group [1].

From 1930 researchers started to use hydrodistention as a treatment for IC/BPS [19]. Va-

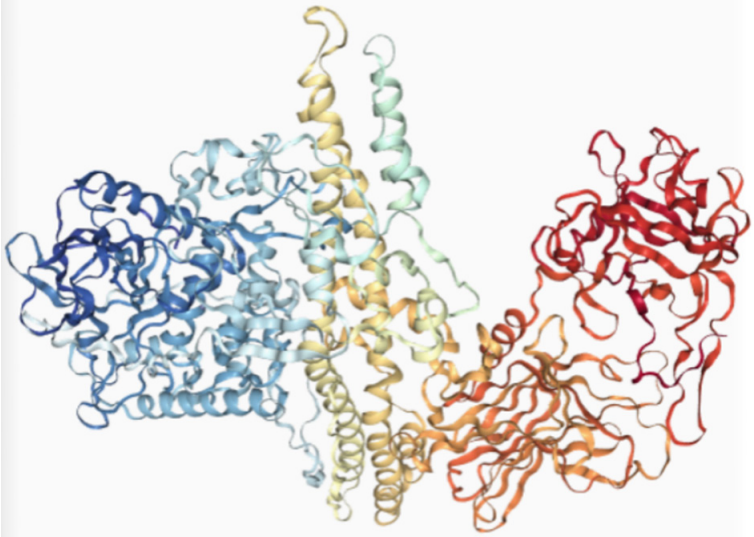

Figure 1. Crystal structure of BTX-A taken from. https://www.rcsb.org/3d-view/3BTA/1.

rious researches proved the positive effect of hydrodistension as a temporary treatment for IC/BPS patients [20, 21]. Most studies performed about effect of BTX-A in these patients use BTX-A injections in combination with hydrodistention. Hydrodistention itself might increase urine Heparin Binding EGF like Growth Factor (HB-EGF), decrease antiproliferative factor and stimulate production of glycosaminoglycan or bladder surface mucin, all that can lead to the reconstruction of the deficient bladder urothelium [21-23]. It is showed in some studies to decrease urothelial dysfunction by modifying microvascularization of the bladder [21, 24]. Hydrodistention also might have inhibitory effects against neurogenic inflammation by degenerating unmyelinated sensory nerve fibers [25]. Though because of shared effective mechanisms that are targeted by both hydrodistention and BTX-A injection, the combination of these two provides higher responses to treatment in IC/BPS patients [26].

Few studies from 2015 till 2018 tried to do BTX-A injections without hydrodistention in order to exclusively focus on BTX-A injection [18, 26]. In 2015 Yoshiyuki Akiyama performed a single-center, prospective, open labeled, randomized comparative study on patients with refractory interstitial cystitis. The distinctiveness of this study was the fact that they tried not to use any hydrodistention or any other intravesical interventions. Patients were randomly divided into a group with immediate injection (group A, n = 18) or a group with 1-month delayed injection (group B, n = 16) of BTX-A after allocation. Second group maintained the present therapies available for IC/BPS for a month and then received the injections. First Statistical analyses for the results carried out at the end of the first month(at this time group B still didn't receive any BTX-A injections) and the second one carried out 1 month later while both groups now received their BTX-A injections and followed up as a single cohort until a year. For study endpoint GRA and symptom changes from baseline were compares a month after allocation by OSSI/OSPI and VAS for pain recorded, also IPSS, OABSS and FVC variables were evaluated. The response rate was significantly higher in group A than group B (72.2% vs. 25.0%, P = 0.01). All symptom measures showed significant improvement in group A than group B. When both groups were combined as a single cohort, the response rate was 73.5% at 1 month, 58.8% at 3 months, 38.2% at 6 months and 20.6% at 12 months. The mean duration of response was 5.4 months. Multivariate analysis showed that past exposure to hydrodistension more than three times correlated with better outcomes. The results mainly put forth that BTX-A injections itself can improve symptoms of IC/BPS while previous hydrodistentions can increase the response rate [26]. On the other hand Hann-chong kou et al. performed a multicenter, randomized, double-blind, placebo-controlled trial on 60 patients (8 males, 52 females, age 50.8 ± 13.9) with IC/BPS refractory to conventional treatment in 2015 using the combination hydrodistention and BTX-A injection. Patients divided into 2:1 ratio. 40 patients undergoing hydrodystention plus suburothelial injections of BoNT-A 100U as Botox group and 20 of them had the equivalent amount of normal saline as N/S group. They measured patient's pain (using Visual Analogue Scale (VAS)), voiding diary and urodynamic variables at 8 weeks after treatment. They indicated that hydrodistension plus suburothelial injections of BoNT-A 100 IU can significantly improve the VAS in compared with control group (-2.6 ± 2.8 vs. -0.9 ± 2.2, P = 0.021). Also there is an increase in Botox group cystometric bladder

capacity at week 8 after treatment with overall success rate of 63% in Botox group and 15% in the N/S group. Bladder tissue obtained from 19 BPS/IC patients before BoNT-A injections and hydrodistension expressed significantly higher nerve growth factor (NGF) levels versus controls, and the level decreased after BoNT-A treatment especially in patients who responded clinically. Also there are no difference in adverse event between the two groups [27].

New methods combining BTX-A and thermo sensitive polymeric hydrogels are in testing and going to be use in urological studies. Variety of thermo sensitive hydro gels can be used to inject the hydrogel in its liquid form and then forms a gel inside the bladder cavity due to body temperature and they have been considered as a vehicle for intra-vesicle drug delivery from 2004 in which Tyagi et al. first used them for instillation of fluoresce in isothiocyanate into mice bladder [28]. It is put forth that using hydrogel as a drug delivery agent can increase the exposure time of BTX-A to the urothelium because of the slow release of BTX-X from the formed hydrogel. Using this method for instillation of BTX-A firstly used by Jan Krhut et al. for treatment of patients with idiopathic overactive bladder (OAB) [29]. In 2017 a prospective, single center, and open label pilot study, by YH Rappaport and his assists used this method for instillation of BTX-A to treat IC/PBS patients, in which showed a significant effectiveness of intra-vesicle instillation of TC-3 Gel/BTX-A. A single dose of 200 U BTX-A premixed with 40 ml TC-3 Gel was instilled into the bladder of 15 severely symptomatic BPS/IC patients (ICSI and ICPI range 12-19 and 12-16, median VAS = 7, M/F = 4/11) using a 12 Fr urethral catheter while the patient was in supine position. Mean baseline VAS decreased significantly in 12 weeks after treatment (6.6 ± 2.7 vs. 5.3 ± 2.8, P = 0.044). Also they reported a significant reduction in ICSI and ICPI after 12 weeks compared with baseline (15.4 ± 2.4 vs. 12.9 ± 4.3, P = 0.004, and 14.8 ± 1.4 vs. 11.9 ± 4.0, P = 0.004). Mean number of voids per night at baseline decreased for 6 weeks (3.3 ± 2.1 vs. 1.8 ± 0.9, P = 0.046) however it returned to baseline level at week 12 [30].

There are also studies focusing on liposome mediated transport of BoNT-A into the epithelium. This was believed to increase the efficacy of BoNT-A treatment due to decreasing the catabolism of BoNT-A protein by Urinary proteases and proteinases, decreasing the dilution of BoNT-A in urine or affecting the poor uptake of BoNT-A across the urothelium due to the animal studies that has been done before hand [12]. On the other hand liposomes can limit the BoNT-A delivery to the mucosa and more specifically deliver it to detrusor muscle so is believed to decrease the chance of incomplete bladder emptying. Yao-Chi Chuang et al. published a prospective multicenter double blind RCT in 2017 focusing on this method. The patients (aged 20 years or above and had failed at least 6 months of conventional treatments) being assigned to three groups. One group being treated with intravesical instillation of lipotoxin (onabotulinum toxin-A 200 U covered in a liposome composed of 80 mg sphingomyelin) (n = 31). The other group treated with onabotulinum toxin-A 200 U in normal saline (n = 28). There was also a control group with instravesical instillation of normal saline alone (n = 31). The procedure of instillation for all three groups was administrated using a 6 Fr Nelaton tube inserted into the bladder and remained for 60 minutes. The changes in OSS, ICSI and ICPI measured 4 weeks after treatment and compared with initial ones. Also, the changes in 3-day voiding diary, VAS and GRA of the patient satisfaction were measured. All 3 groups showed an improvement in pain scale and OSS after treatment. Instillation of Lipotoxin also decreased OSS (7.38 ± 8.75), ICSI (4.00 ± 4.28), ICPI (3.35 ± 5.11), and VAS pain scale (1.64 ± 2.52) and increase GRA (1.35 ± 1.28) in a statically significant manner. However there was no significant adverse events in any of the groups [3].

Discussion

Since very first usage of BTX-A in IC/PBS patients, applications showed an increase in use of this method. Intravesical BTX-A injections are going to be widely used in urodynamic studies and is proved by DHIC and it has been considered as a standard treatment for patients who have an inadequate response to other treatments according to AUA and EAU guidelines [10, 31].

BTX-A decreases the ICPI and ICSI most studies. Since ICPI and ICSI have been widely recognized as reliable, valid, and responsive instruments to assess IC/PBS symptoms [32] both BTX-A injection and instillation can significantly influence subjective symptoms.

BoNT-A injection to the bladder body or trigone both provides effective therapeutic results in

IC/BPS patients with acceptable adverse events, but. However, improvements in IC symptoms and urodynamic parameters after BTX-A injections are permeant and mostly lasts no more than 12 weeks. Since the pathogenesis of IC/BPS remains unclear, the current goals of treatment are purely based on symptomatic relief which is fulfilled with BTX-A.

Instillation of BTX-A and delivering it using hydrogel gelation and liposome-encapsulation is a less invasive and more convenient method for slow releasement of BTX-A which is being used in some studies [3, 30, 33, 34]. Intravesical instillation of the TC-3 Gel/BTX-A mixture is feasible and safe, which is accompanied by mild and temporary adverse events, and no worsening of IC/BPS symptoms. On the other hand, Liposome-encapsulated BTX-A failed to demonstrate a positive proof-of-concept compared to BTX-A injections or even placebo in treatment for IC/BPS. Nevertheless, intravesical instillation of lipotoxin is safe, with no increase in risk of retention or increase in residual urine volume.

Conclusion

Despite the large placebo effect in treatment of IC/BPS, BTX-A showed to improve IC/BPS symptoms periodically and thereby it is needed to repeat the injections when symptoms reoccur. Studies focusing on site of injection showed the fact that there is no difference in whether BTX-A is injected to body or trigone but there is a need on further large-scale studies over this subject. Hydrodistention also showed to increase the therapeutic effect of BTX-A for IC/BPS patients. We also recommend that further well-designed RCTs are necessary to show strong evidence for the efficacy of BTX-A, evaluate dosing, number of site injections and reinjection effectiveness. Also new methods such as gel and liposomal delivery of the toxin need for further assessments in large scale RCTs. There is also a need for studies on pathogenesis and therapeutic basis of IC/PBS to improve our understanding of this disease and how it can be treated.

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Disclosure of conflict of interest

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