Current Bladder Dysfunction Reports (2023) 18:147–153
https://doi.org/10.1007/s11884-023-00695-6

BPS/INTERSTITIAL CYTITIS (D CASTRO-DIAZ AND Y IGAWA, SECTION EDITORS)

Botulinum Toxin Therapy for Bladder Pain Syndrome/Interstitial Cystitis

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Accepted: 26 September 2022 / Published online: 15 February 2023

Abstract

Purpose of Review Bladder pain syndrome (BPS)/interstitial cystitis (IC) can also be classified as either non-ulcerative or ulcerative, corresponding to the characteristic cystoscopic findings under hydrodistention. Promising therapeutic effects, including decreased bladder pain, have been reported from recent clinical trials using botulinum toxin A (BoNTA) for the treatment of BPS/IC. This review summarizes the current state of the literature on the underlying mechanisms of BoNTA therapy in BPS/IC as well as new forms of its application.

Recent Findings BoNTA has its effect in the central nervous system in the afferent nerves as well as in the bladder wall. Besides the well-known effects of BoNTA in the nervous system, pain control as well as reduction of urinary urgency in BPS patients could be achieved by mast cell stabilization effecting histamine release as well as modulation of TRPV and PGE_2 pathways, among other systems. In addition, new forms of BoNTA administration have focused on intravesical instillation of the drug in order to circumvent bladder wall injections. Hyperthermia, intravesical hydrogel, and lysosomes have been studied as new ways of BoNTA application in BPS/IC patients. From the available studies, bladder instillation of BoNTA in combination with EMDA is the most promising and effective novel approach.

Summary The most promising novel application methods for BoNTA in patient with BPS/IC are bladder instillations. Future research needs to point out if bladder instillations with BoNTA with some form of bladder absorption enhancement such as hyperthermia or EMDA would be able to replace BoNTA injections in patients with BPS/IC

Keywords Botulinum toxin · Bladder pain syndrome · Interstitial cystitis · Botox

This article is part of the Topical collection on *BPS/Interstitial Cytitis*

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Introduction

Bladder pain syndrome (BPS) is defined as "bladder filling accompanied by suprapubic pain and intensified daytime and night time frequency in the lack of urinary infection, or other pathologies of the lower urinary tract" [1].

Chronic pelvic pain syndrome (CPPS) is defined by pain in the pelvic area that can have different aetiologies. This can be due to urologic, gynaecologic, musculoskeletal, gastrointestinal, neurologic, and autoimmune or rheumatologic diseases with dramatic psychosocial impacts [2–4]. Patients with predominant bladder pain symptoms without any other diagnosis are often referred to as BPS patients. Another often used term is interstitial cystitis (IC) which refers to a subgroup of patients with BPS who have Hunner's lesion or histological changes in their bladder biopsies.

CPPS, BPS, and IC are linked but are not synonyms. They are often even defined slightly different by different societies

or authorities. According to the definition of the International Society for the Study of Interstitial Cystitis/Bladder Pain Syndrome (ESSIC), BPS/IC is defined by the chronic pelvic pain that a patient feels it is related to the bladder, with urgency and/or frequency [5].

BPS/IC is more common in women than men, though it may be confused with chronic prostatitis among men [6].

BPS/IC can also be classified as either non-ulcerative or ulcerative, corresponding to the characteristic cystoscopic findings under hydrodistention [7]. Due to their distinct underlying patho-physiologies and approaches regarding treatment, non-ulcerative BPS/IC and ulcerative are seen as two unique conditions [8]. Those suffering from ulcerative BPS/IC tend to be patients of older age with a smaller bladder capacity and more bladder pain in comparison to those suffering from non-ulcerative BPS/IC. Between 10 and 20% of BPS/IC patients suffer from ulcerative BPS/IC [9].

Subsequently, the majority of treatment methods used are off-label as both the diagnosis and treatment are challenging. A number of invasive treatments have been identified. Among them are intravesical injections of botulinum toxin A [10].

Clinical Efficacy of Botulinum Toxin A BPS/IC

Promising therapeutic effects, including decreased bladder pain, have been reported from recent clinical trials using botulinum toxin A (BoNTA) for the treatment of BPS/IC [10].

Botulinum toxin A selectively regulates sensory function, inflammation, and glandular function, suppresses detrusor overactivity, and disrupts and regulates neurotransmission. Since botulinum toxin A has been known to possess sensory inhibitory effects and anti-inflammatory effects alongside motor effects, it has been used as a treatment method for BPS/IC and overactive bladders (OAB). Consequently, the therapeutic period was observed to be longer with several Botox injections than with a single injection [11].

In another study, it was discovered that ulcerative BPS/IC did not respond well to four recurring injections of 100 U of a BoNTA, once every 6 months [12]. Though this research indicates that BoNTA treatment is perhaps not suitable for ulcerative BPS/IC, a Portuguese group discovered that Botox trigonal injection provided satisfactory results in subjects with ulcerative BPS/IC and that treatment results regarding symptom intensity do not differ among ulcerative and non-ulcerative BPS/IC [13]. A point to be considered is that ulcerative BPS/IC is not properly defined and thus treatment outcomes with regard to Botox injections in ulcerative and non-ulcerative BPS/IC may not be properly compared. Regardless, considering the weak results of conventional treatment methods with ulcerative BPS/IC, ulcerative BPS/IC should be viewed as a different disease from non-ulcerative BPS/IC.

Recent published data support the effectiveness of Botox in relieving bladder pain and inconvenient bladder symptoms in subjects with refractory BPS/IC. Short-term success could be achieved in bladder pain, frequency, and bladder capacity with Botox injections. Long-term therapeutic results are not reached and the application of Botox for BPS/IC has not yet been approved, though repeat Botox injections may have long-term effective outcomes [11].

Systematic reviews and meta-analyses confirm the promising results of BoNTA in reducing pain intensity in BPS/IC patients. However, the number of studies included in the first evidence-based meta-analysis was limited to five randomized clinical trials (RCT) comprising 252 patients (133 subjects in the intervention group vs. 119 cases in the control group), with a varied injection dose between 50 and 200 U. The results showed that VAS score and Interstitial Cystitis Problem Index (ICPI) as well as frequency were improved after the intervention. The other reported outcomes (Interstitial Cystitis Symptom Index (ICSI), nocturia, maximal urinary flow rate (Qmax), and functional bladder capacity (FBC) were not statistically different between the two groups [14]. Another systematic review included only seven RCTs and one retrospective study. The results revealed that despite a slight increase in PVR levels, Botox® injections reduced pelvic pain, ICPI, and ICSI. Except for a significant improvement in daily urinary frequency and maximum cystometric capacity, no difference was observed in Qmax, dysuria, and urinary tract infection (UTI) rate following treatment [15].

In a more recent systematic review by Giannantoni et al., comprising 12 RCTs, the results showed a change in ICSI in ten trials, in ICPI score in nine trials, in pain score based on VAS in seven trials, in the Likert scale in two trials, in urinary frequency in 8 trials, Qmax in 6 trials, in PVR in 7 trials, and FBC in 7 trials. Based on the meta-analysis results, a moderate effect size, considering standardized mean difference, in VAS changes for pain and urinary frequency was observed. Besides, a small to moderate SMD was detected for changes in ICSI and ICPI scores. In terms of nocturia and functional bladder capacity and Qmax, there were no changes in SMD. Larger SMD was detected only for changes in PVR, which, as expected, is a possible complication of neurotoxin injection into the bladder wall and represents a side effect [16].

There is great variation in neurotoxin doses, injection methods, and injection sites in RCTs included in the systematic reviews. In fact, in 11 clinical trials, BoNTA was injected in different doses (50–300 units) and in different locations (Trigone: 3 studies, whole bladder wall: one study, out of Trigone: 3 studies, and bladder neck in one study). Abobotulinum A (Abobot/A or Dysport®, 500 U) was used as the active treatment in a single clinical trial. Recently,

the authors reported the outcomes of 300–500 U Dysport® intravesical injection in refractory BPS/IC. The results revealed that most cases had good or intermediate improvement (93%) based on the Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) questionnaire results [17].

In addition, the depth of injections into the bladder wall varied between the included trials. Regarding the injection site, BoNTA was injected into the detrusor or sub-urothelially in four clinical trials. In some cases, BoNTA was administered under general anesthesia (3 trials), spinal anesthesia (1 trial), or local anesthesia (1 trial), and in the remaining studies, the types of anesthesia were not described. There was also a great deal of variation in the factors used in the control groups. In different studies of hydrodistension dilation, normal saline, normal saline plus hydrodistension, Calmette-Guerin bacillus (BCG), lipotoxin, and pentosan polysulfate sodium instillation were reported. In addition, in one study, the control group included patients who received Onabot/A delayed injections compared with patients in the active group who received neurotoxin A immediately [18].

Considering the adverse events including UTI, urinary retention, pain, and haematuria, some researchers attempt to show the role of lipotoxin on the success rate and reduce the side effects. However, to date, lipotoxin has failed to demonstrate a positive proof of concept compared to BoNTA or placebo [19].

To support BoNTA as a standard treatment for patients with BPS/IC, and to know if this method is effective or not, further randomized, placebo-controlled studies (RCTs) with larger patient samples are needed. The studies should aim to clarify how to inject it (injection into the detrusor muscle or in the bladder urothelium), whether or not use other toxin types than Botox® as well as side effects.

Mechanism of Action of Intravesical BoNTA: How Might It Contribute in the Treatment of BPS/IC?

Our understanding of the analgesic mechanism of action of BoNTA in the bladder involves various interactions in nociception pathways, mediated by effects on peripheral sensory nerves and on the central nervous system but, also, by direct histological change [20, 21]. The current notion is largely extrapolated by findings of preclinical studies. On the level of peripheral sensory nerves, BoNTA inhibits the release of urothelial ATP in animal models of chronic bladder inflammation [22], which activates P2X3 receptors, implicated in sensory and pain pathways [23, 24]. BoNTA has also been associated with downregulation of TRPV1 in suburothelial fibers, a tension and pain receptor [25, 26], as well as with a reduction of nerve growth factor (NGF) [27], which has been shown to elicit hyperalgesia and promote neuronal growth and sprouting [28]. In animal models of bladder pain, acute or chronic inflammation, intravesical BOTOX administration reduced not only the release of nociceptive neurotransmitters such as calcitonin gene-related peptide (CGRP) and substance P (SP), but also the histological inflammation [29–31]. The anti-inflammatory action of BOTOX is also supported by studies demonstrating a reduction in COX-2 and EP4 expression in animal bladder and spinal cord [32]. Further evidence for the involvement of central pathways in the mechanism of action of Botox was provided by animal models of CYP-induced cystitis: Intravesically administered Botox reduced the *c-fos* expression in the L6-S1 dorsal root ganglia [33], while the intrathecal administration of BoNTA improved bladder function and pain-associated behavior, possibly via reversal of the effect of CYP on inflammatory markers such as *c-Fos*, *p-ERK*, and CGRP [34]. Finally, intravesical administration of BoNTA using low-intensity extracorporeal shock wave treatment was associated with significantly lower expressions of TNF-α and IL-6 and significantly reduced submucosal edema and inflammatory cell infiltration [35]. Further research is warranted to completely unveil the perplexed analgesic action of BoNTA in human urological pain syndromes and BPS/IC.

Novel Approaches to Administer BoNTA into the Bladder Wall

Cystoscopic-guided BoNTA injections into the bladder wall have been used for a variety of bladder dysfunctions. For BPS/IC, bladder wall injections have been well described [14]. Intratrigonal [36] and trigone sparing techniques [37] have been described. Alternative techniques of intravesical administration of botulinum toxin have evolved in recent years, aiming to reduce the adverse effects and improve the acceptability of this agent.

New ideas on BoNTA administration predominantly focus on intravesical instillation of the drug in order to circumvent bladder wall injections [38, 39]. The potential benefits of this application strategy would be a less invasive procedure and a more homogenous spread of the toxin across the bladder wall surface. The main challenge for intravesical BoNTA instillations to work is getting an adequate concentration of the drug across the urothelial barrier.

There is some evidence that BoNTA inhibits COX-2 and EP4 expression in the bladder, interacts with SNARE proteins in the urothelium, and modulates urothelial ATP release [32, 40–42]. It is currently unknown if this effect would be clinically relevant in BPS/IC patients, but ATP and purinergic signaling are considered one of the primary afferent signaling pathways within the bladder [40]. If clinically relevant, an inhibitory effect on urothelial afferent pathways

would give more rationale for intravesical BoNTA instillation for BPS/IC.

Shatoury et al. explored the use of hyaluronan-phosphatidylethanolamine as a vehicle for BoNTA to improve efficacy of intravesical application of BoNTA and demonstrated a comparable reaction in SNAP25 immunostaining compared to injected BoNTA in a rat model [43].

Another potential route for improving BoNTA incorporation into the bladder wall is to make the urothelium more permeable before BoNTA is applied. To accomplish this, low-energy shockwave treatment combined with BoNTA instillation was investigated in a rat model by Chuang et al. and showed improvement of urodynamic parameters and decreased SNAP and COX-2 expression compared to controls [44]. Shock wave therapy has been found to reduce the inflammation in bladder using another rat model [45]. In a prospective randomized double-blind placebo-controlled trial, low-energy shock wave treatment imparted benefit to the patients with bladder pain syndrome [46].

Hyperthermia could also be an interesting option to explore, since it is being applied for intravesical chemotherapy in bladder cancer [47, 48]. Heated mitomycin C increases the cytotoxic effect by temporarily increasing the permeability of urothelial cell membranes and disruption of cell junctions [47, 49]. This is currently done with radiofrequency (microwave)-heated catheter systems that heat the bladder up to 45–46 °C for 1 h [50]. Applicability for intravesical BoNTA treatments would depend on the stability of the BoNTA compound under hyperthermic conditions and efficacy/burden ratio of a hyperthermia treatment compared to the traditional injection technique.

Electromotive drug administration (EMDA) is a minimally invasive method of intravesical instillation of therapeutic agents using short burst of electromotive force. It involves a combination of iontophoresis, electrophoresis, and electroporation to deliver drugs into deep tissue layers using an electrical current created between two electrodes [51]. This can be done under local anesthesia using lignocaine and epinephrine. It utilizes a system containing a DC current generator and catheter electrodes. This technique has been used to deliver intravesical agents for a variety of clinical conditions such as inflammations of the urinary bladder and the prostate, cancer of the urinary bladder, and overactive bladder [52]. In a systematic review, six studies including 89 patients with bladder pain syndrome, treated with administration of botulinum toxin using EDMA, were identified [53]. These studies report promising results but the limitations of the included studies are the small number of patients, with the non-randomized design.

Several other techniques are being investigated in clinical studies [43, 44, 54]. In the transcellular approach, bladder instillation of drug-containing liposomes is used to cross the urothelial cellular membranes through normally occurring endocytosis processes [54]. Botulinum toxin is a large molecule and cannot penetrate the urothelium to act on the target tissue. Therefore, it has been encapsulated into a liposome to be used as an intravesical instillation [55]. Chuang et al. investigated this with BoNTA in a clinical RCT in 62 OAB patients with a significant effect on symptoms [56]. However, an additional RCT from the same group evaluating 31 BPS/IC patients could not show significant improvement [19]. Intravesical liposomal botulinum toxin has been compared with oral PPS in patients with BPS/IC and found to have equivalent results [57]. In a prospective multicentre double-blind, randomized trial, bladder instillation of liposome encapsulated onabotulinum toxin A was found to improve symptoms in BPS/IC [19].

Intravesical hydrogel is another possible way of drug administration. The complex urothelial layer poses difficulties in intravesical drug administration. Drug delivery systems based on the hydrogel reservoirs have been studied [58]. Hydrogels are three-dimensional network of hygroscopic polymers which act as reservoir of drug [59]. In the urinary bladder, intravesical use of hydrogel for drug delivery can prolong retention time in the bladder giving an opportunity for sustained drug release and maintaining drug concentration resulting in better therapeutic efficacy [39]. A pilot study in patients with overactive bladder concluded that intravesically instilled botulinum toxin embedded in inert hydrogel could be a good alternative to intravesical injections [60]. In a single-arm pilot study, BPS/IC patients were treated with intravesical administration of TC-3 hydrogel embedded BoNTA [61]. Despite lack of a placebo arm, it was concluded that bladder pain and urinary frequency significantly decreased at 12 weeks follow-up. Although preliminary studies revealed promising therapeutic outcomes, only few clinical trials with limited patients have been conducted.

Discussion

Even though repeat injections have shown benefit in cases of refractory BPS/IC [62], there is a subset of patients who may not benefit, especially the ones with ulcerations [12]. Long-term compliance for intravesical botulinum toxin has been poor due to recurrent retention of urine necessitating intermittent catheterizations and voiding LUTS [63]. In Fig. 1, different levels of effect of BoNTA have been summarized. BoNTA has its effect in the central nervous system in the afferent nerves as well as in the bladder wall. Besides the well-known effects of BoNTA in the nervous system, pain control as well as reduction of urinary urgency in BPS patients could be achieved by mast cell stabilization effecting histamine release as well as modulation of TRPV and PGE_2 pathways, among other systems.

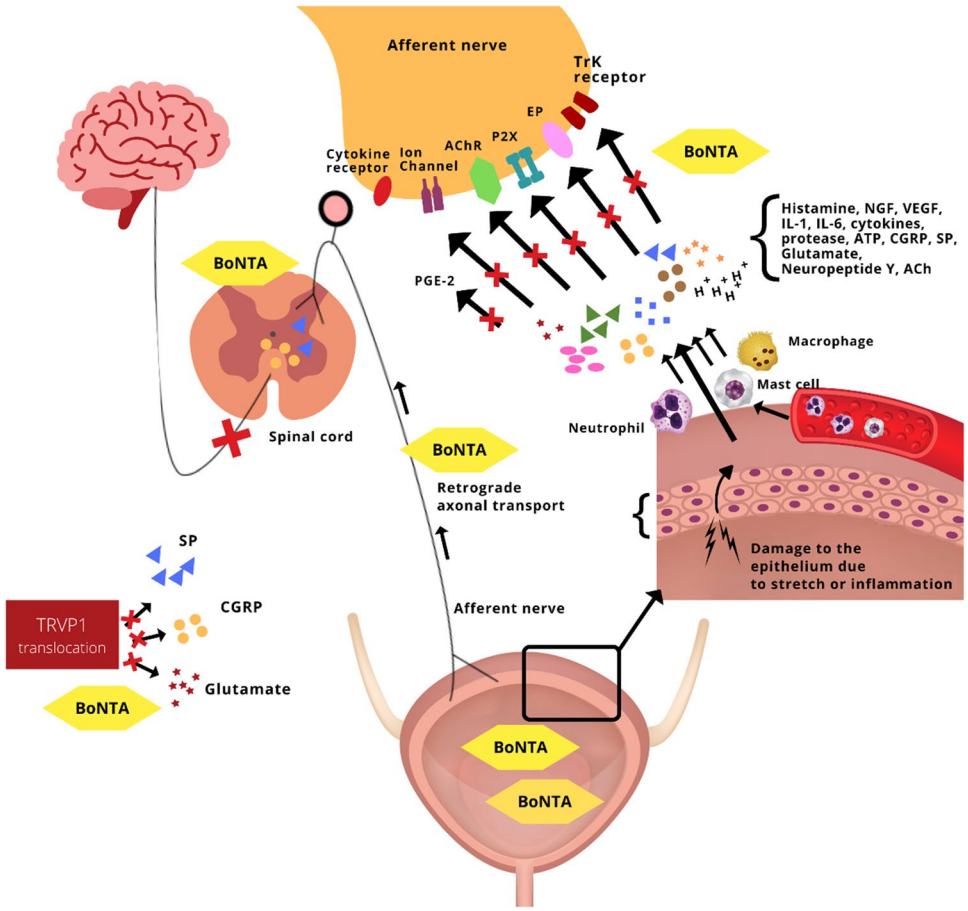

Fig. 1 A summarizing cartoon about how BoNTA might have its effect in the treatment of BPS

New forms of BoNTA administration have focused on intravesical instillation of the drug in order to circumvent bladder wall injections. From the available studies, bladder instillation of BoNTA in combination with EMDA is the most promising and effective novel approach although most studies are limited with a small number of included patients and have a non-randomized results. Hence, more high-powered randomized studies are needed to confirm the promising results of BoNTA bladder instillation with EMDA.

Conclusion

The most promising novel application methods for BoNTA in patient with BPS/IC are bladder instillations. Future research needs to point out if bladder instillations with BoNTA with some form of bladder absorption enhancement such as hydrogel, liposomes, hyperthermia, or EMDA would be able to replace BoNTA injections in patients with BPS/IC.

Funding Open Access funding enabled and organized by Projekt DEAL.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing Interests The authors declare no competing interests.

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