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NEUROGENIC BLADDER (C POWELL, SECTION EDITOR)

Botulinum Toxin for Neurogenic and Non-neurogenic Bladder Pain

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Abstract

Purpose of Review The use of botulinum toxin in managing urinary incontinence has been well established. Given the expanding indications for this agent for several neuromuscular disorders, its role in managing the symptoms associated with interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic pelvic pain syndrome (CPPS) is evolving. In this review article, we examine the current literature on outcomes after botulinum toxin injection in patients with these conditions, as well as recent developments in mechanism of delivery.

Recent Findings The change in pain scores after injection in IC/BPS patients is inconsistent, as it has been used in combination with and without other interventions, such as hydrodistension. Pooled studies favor the use of botulinum toxin, but the findings are not significant to justify its use as a first-line treatment for IC/BPS. The initial hope that botulinum toxin would improve CPPS by addressing hypertonic pelvic floor dysfunction has been tempered by several studies showing no significant reduction in pain scores after injection compared to placebo.

Summary Several studies have shown there to be a therapeutic benefit for pain management in IC/BPS, particularly in those without Hunner's lesions. Meta-analysis suggests that higher dose may further improve pain scores, but side effects of urinary retention may limit its applicability. This effect does not appear to be dependent on how the toxin is injected (trigone vs non-trigone). Future use of intravesical liposomes to deliver botulinum toxin shows promise in administration of the agent in a non-invasive manner.

Keywords Botulinum toxin · Interstitial cystitis · Chronic pelvic pain · Therapy · Pelvic floor dysfunction · Bladder capacity

Introduction

According to the American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU), interstitial cystitis/bladder pain syndrome (IC/BPS) is defined as "an unpleasant sensation (pain, pressure, discomfort), perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks in duration, in the absence of infection or other identifiable causes [1]." Its incidence ranges from 2.9 to 4.2% with a higher prevalence in women than men [2]. No specific etiology for IC/BPS has been found, and it is uncertain whether IC/BPS is a primary disorder of the bladder or a secondary effect from another cause. Because of its associations with systemic comorbidities such as anxiety, depression, fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, Sjogren's, chronic headaches, and vulvodynia, IC/BPS is thought to be part of a wider systemic dysregulation [3, 4]. Moreover, its overlap with chronic pelvic pain syndrome (CPPS), defined as persistent pain for more than 6 months in the pelvic region associated with lower urinary tract, gynecological, pelvic floor, or sexual dysfunction, also suggests IC/BPS may be a syndrome and not a singular disease. Though the incidence of CPPS ranges from 6 to 27% worldwide [5], Suskind et al. found that there was a 17% overlap between the two syndromes [2]. There is no definitive etiology for CPPS, but one proposed pathophysiology is the spasticity of the pelvic floor

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muscles due to psychological or pathological disorders [6]. This chronic increased pressure can lead to vessel compression and muscle ischemia with the release of bradykinin and stimulation of the nociceptive receptors [7]. Given that the pelvic floor muscles are intimate with urinary, vaginal, and rectal organs, its dysfunction can result in pelvic, specifically bladder, pain.

Clinicians who treat IC/BPS and/or CPPS recognize the therapeutic challenges of these conditions, which often require a multimodal approach, including a holistic approach to mind and body. AUA guidelines place conservative treatment such as stress management, counseling, physical therapy, and either oral or intravesical pharmacological agents as first- and second-line therapies for IC/BPS [8]. If unresolved, patients can proceed with cystoscopy, hydrodistention, and fulguration of Hunner's ulcers if present. Similarly, European Urological Association (EUA) guidelines suggest behavioral modifications, medical therapy, and/or nerve blocks as initial treatment regimens for CPPS [9]. If refractory to these, intradetrusor or myofascial injection of botulinum toxin and neuromodulation are considered next line options for both IC/BPS and CPPS [8, 9].

The aim of this paper is to evaluate the role of botulinum toxin in alleviating bladder pain as a direct bladder treatment, or indirectly by addressing high-tone pelvic floor muscle dysfunction as a source of pelvic pain.

Mechanism of Action

Botulinum toxin is an organic macromolecule (300–900 kD) produced by the anaerobic bacteria *Clostridium botulinum* [10]. This protein complex consists of a physiologically active 150-kD neurotoxin bonded to nontoxic accessary proteins (NAPs). This 150-kD neurotoxin itself consists of a 50-kD light chain connected via a disulfide bond to a 100-kD heavy chain [11]. At the presynaptic cleft, the 100-kD heavy chain binds to the synaptic vesicle protein 2 and facilitates endocytosis of the botulinum toxin [12]. Once intracellular, the 50-kD light chain then inhibits the function of synaptosome-associated protein 25 which normally induces exocytosis of acetylcholine neurotransmitters [13]. With the lack of acetylcholine at the neuromuscular junction, muscle paralysis results.

There are three mechanisms of action in which botulinum toxin can reduce pain. Firstly, with the lack of stimulation from the neurotransmitters, spasmodic muscles are medically induced to relax, thus reducing pain. Secondly, animal studies suggest that botulinum toxin reduces expression of nociceptive neurotransmitters and receptors. Glutamate expression, an excitatory neurotransmitter known to be critical in pain pathways, was downregulated in human and rat skin after botulinum injection [14]. In animal models, CGRP, substance P, and ATP which are well-studied nociceptive neurotransmitters were shown to be significantly reduced after botulinum injection [15–20]. Moreover, expressions of prominent nociceptive receptors such as TRPv1 and P2×3 have been shown to be significantly reduced in overactive patients after botulinum injection via bladder biopsy [21, 22]. Lastly, repeated botulinum toxin injections reduce mast cells, cyclooxygenase 2, and prostaglandin E2 receptors, thus decreasing inflammation and subsequent pain [23, 24].

Though eight serotypes (type A-H) [10] and over 40 subtypes [25] are known, the two clinically available botulinum toxin isoforms are A1 (BoNT-A) and B1, with A1 being commonly used due to its duration and potency [26]. The commercial forms of injectable botulinum toxin A1 include onabotulinum toxin A (ONA; Botox/Vistabel, Allergan Inc., Irvine, CA, USA), abobotulinum toxin A (ABO; Dysport/Ipsen Limited, Slough Berkshire, UK), and incobotulinum toxin A (INCO; Xeomin/Bocouture, Merz Pharmaceuticals GmbH, Frankfurt, Germany). One novel delivery system is the liposome-encapsulated botulinum toxin which utilizes endocytosis to deliver drugs intracellularly, thus reducing the risks associated with submucosal injections [27]. These variations of neurotoxin A differ in their NAP compositions with the exception of INCO, which consists of only the free active 150-kD neurotoxin. Because potency is dependent on the quantity of available 150-kD active moiety, the conversion ratio between the three variations are different with a 1:1 ratio for ONA to INCO and 1:3 for ONA to ABO [10]. Over time, development of neutralizing antibodies, especially against the NAPs, can decrease efficacy [28]. Cost is also varied with ONA as the most expensive at $49,337 per quality-adjusted life year (QALY) compared to $36,678/QALY for ABO and $27,548/QALY for INCO [29].

Early Uses of BoNT-A

Clinical use of BoNT-A was first used in the late 1960s to treat strabismus in rhesus monkeys by Dr. Alan Scott [30]. Since then, its indications has expanded widely to include treatment for urological diseases such as detrusor-sphincter dyssynergia [31], neurogenic detrusor overactivity with urge urinary incontinence [32, 33], and overactive bladder refractory to anticholinergic therapy [34, 35].

BoNT-A as Bladder-Directed Therapy

Initial Studies

Despite the versatility of botulinum toxin as a neuromuscular agent, there is conflicting data on the efficacy of BoNT-A injections in addressing bladder pain in patients with

IC/BPS. In one of the earliest randomized controlled trial (RCT), Kuo and colleagues compared clinical and functional outcomes of patients who underwent cystoscopic hydrodistention (HD) only ($n=23$), HD + 100 IU ONA ($n=29$), or HD + 200 IU ONA ($n=15$) [36]. At 3 months, 80% of HD + 200 IU ONA patients and 72% of HD + 100 IU ONA had a 5 ("markedly improved") or a 4 ("moderately improved") in pain reduction on the global response assessment (GRA) as compared to 48% of HD only patients ($p=0.032$). A similar pattern was seen with the pain visual analog scale (VAS) (55% vs 39% vs 18%, $p=0.007$), with an increase in maximum cystometric capacity (MCC) (156.4 cc vs 79.5 cc vs 11.8 cc) [36].

However, other early studies suggest that placebo effects may play a large role in pain reduction. In 2012, Kasyan et al. reported a VAS score reduction from 9.3 ± 0.9 at baseline to 5.8 ± 2.4 at 3 months in patients who underwent 100 IU of BoNT-A injection, compared to a change from 8.7 ± 1.2 to 6.1 ± 2.8 in patients with HD ($p>0.05$). The reduction in O'Leary-Sant scores (OLS) was also similar in both groups (14.5 ± 2.3 at baseline to 9.4 ± 2.9 at 3 months vs 13.8 ± 3.7 at baseline to 8.8 ± 3.3 at 3 months, $p>0.05$) [37]. Manning et al. evaluated the same question but used 500 IU of ABO instead. In a cohort of 54 patients, those who underwent HD ($n=21$) reported a change of -1.5 on their OLS compared to 3.7 in patients who underwent HD + 500 IU of ABO ($n=16$, $p=0.12$) at 3 months. MCC increased by 19.6 ml (-2.7 to 41.8) in the treatment group compared to a reduction of 18 ml (-85.4 to -49.5) in the placebo group ($p=0.27$) [38]. Gottsch et al. investigated not only a different injection site—periurethral instead of intradetrusor—but also at a lower dosage of 50 IU. In a small RCT of 20 patients, there was not a significant change from baseline in VAS scores for the BoNT-A group (-0.3) nor were there differences in the Chronic Prostatitis Symptoms Index (CPSI) scores between the experimental and control groups at 3 months ($p=0.97$) [39].

Current Literature

In more recent literature, studies suggest a clinical benefit in pain reduction with BoNT-A injections. In a RCT of 60 patients who received either HD + 100 IU ONA versus normal saline injections at 20 sites, Kuo et al. reported a significant decrease in VAS at 8 weeks between the two groups favoring BoNT-A (-2.6 vs -0.9, $p=0.021$). However, there were no differences in OLS or GRA. On urodynamics, there was an average increase of 67.8 ± 164.3 ml in maximum cystometric capacity compared to a mean reduction of -45.4 ± 138.5 ml in the placebo group ($p=0.020$) [40].

Similarly, in a smaller study of 19 patients, Pinto et al. reported an average VAS reduction of -3.6 ± 2.5 in patients who received 100 IU of ONA ($n=10$) compared to -1.6 ± 2.1 in the control group ($n=9$) at 3 months ($p<0.05$) [41]. Difference in OLS (-9 ± 4.7vs -7.1 ± 4.6, $p<0.05$) and treatment benefit scale (1.9 ± 0.9 vs 3.1 ± 0.8, $p<0.001$) was even more pronounced.

The presence of Hunner's lesions may also impact clinical response. In a cohort of 44 patients, Lee et al. [42] evaluated the clinical and functional outcomes of patients with Hunner's lesion (HL) IC ($n=10$) compared to non-HL IC ($n=30$) after serial intradetrusor injections of 100 IU of BoNT-A every 6 months for 2 years. With success defined as GRA > 2 at endpoint, those with non-HL were further subcategorized into those who had a GRA ≥ 2 ($n=15$) and those with GRA ≤ 2 at the end of the study. At 2 years, there were no HL patients who achieved GRA > 2 compared to 50% of those with non-HL IC. Higher OLS and VAS scores reductions were seen in those with non-HL IC than HL ($p=0.001$, $p=0.062$, respectively), with non-HL IC with GRA ≥ 2 doing the best ($p=0.004$, $p=0.136$, respectively). Cystometric capacity increased on average 69 ml for non-HL IC with GRA ≥ 2, 64 ml for non-HL IC with GRA < 2, and decreased by 13 ml for HL IC. Overall, the authors concluded that repeated BoNT-A may benefit those with non-HL IC but not those with HL.

Data suggests that location of intradetrusor injections does not affect outcomes. In 2020, Evans et al. randomized 26 patients to 100 IU BoNT-A at 10 sites at the trigone or trigone sparing [43]. At 3 months, there were significant improvements in both arms on OLS without differences between the two templates. Similarly, Jiang et al. randomized 39 patients to 100 IU BoNT-A at 20 bladder body sites ($n=20$) or 10 trigone sites ($n=19$) [44]. Both groups had significant improvements in OLS, VAS scores, and functional bladder capacity (FBC) from baseline. There were no differences between the two groups, with a GRA ≥ 2 achieved in 45% of the bladder body site group compared to 52.6% in the trigone site group ($p=0.63$).

Lee et al. examined long-term efficacy in 104 patients with IC/BPS who had HD + 100 IU BoNT-A every 6 months for 2 years or until the patient wishes to discontinue. At 6 months, there were significant improvements in the OLS (23.7 ± 6.1 vs 16.6 ± 8.9, $p<0.0001$), VAS (5.2 ± 2.4 vs 3.5 ± 2.5, $p<0.0001$), FBC (129.1 ± 75.0 vs 177.7 ± 85.0, $p<0.0001$), and GRA (1.31 ± 0.97, $p<0.0001$). While only 59/104 patients chose to remain in the study, the outcome parameters were sustained in this group (OLS: 15.2 ± 8.9, VAS: 2.9 ± 2.3, GRA: 1.8 ± 1.1, FBC: 226.9 ± 108.8 ml, $p<0.0001$) [45•]. PVR was low in this cohort -17.1 ± 38.1 ml at baseline after 1 injection, 42.4 ± 77.9 ml at 6 months, 47.8 ± 84.7 ml at 18 months and 64.1 ± 114.2 ml at 24 months ($p=0.015$) [45•]. Rates of UTI ranged from 5.9 to 13.9% after each treatment.

Despite these positive findings, the effect of BoNT-A in reducing the pain component of IC/BPS is inconsistent

across studies. Gao et al. evaluated VAS and OLS in 124 patient who either had HD + Cystistat instillation or HD + 100 IU BTX-A (Lantox; Lanzhou Institute of Biological Products in China, Lanzhou, China). At 3 months, the OLS decreased in the HD + BTX-A group from 34.2 ± 1.7 to 31.2 ± 2.4 compared to 34.2 ± 1.5 from 34.7 ± 1.5 for the HD + C group ($p < 0.05$). Although the VAS score decreased significantly from baseline in both the HD + BTX-A (9.4 ± 0.9 to 8.1 ± 1.3, p < 0.05) and HD + Cystistat (9.2 ± 0.8 to 7.9 ± 1.3, $p < 0.05$) groups at 3 months, the scores did not differ significantly [46].

In 2016, Shim and colleagues conducted a systematic review and meta-analysis on the efficacy of BoNT-A for IC/BPS that included five randomized controlled trials between 2009 and 2015 [36–40, 47]. The combined cohort was 252 subjects with 133 in the treatment group and 119 in the control. The difference in pooled overall mean change of OLS (95% CI − 0.97, − 0.30) and VAS (95% CI − 0.74, − 0.23) between the two groups was statistically significant at − 0.63 and − 0.49, respectively, favoring intervention. Subgroup analysis of dosage showed improvements in OLS of − 0.49 (95% CI − 0.92, − 0.05) for 100 IU and − 0.87 (95% CI − 1.38, − 0.36) for 200 IU. However, the difference in FBC was not significant (pooled overall SMD: 0.29, 95% CI − 0.05, 0.63). There were considerable adverse effects such as dysuria (31% vs 4.7%, $p = 0.001$), elevated PVR (8.3% vs 0%, $p = 0.094$), and urinary retention (7.1% vs 0%, $p = 0.095$). Study design and outcome measures are summarized in Table 1.

In a 2021 systematic review of the literature on BoNT-A use in CPPS, Parson et al. evaluated a total of 16 studies—11 RCT, 5 non-randomized study (NRS)—from 2009 to 2020 [48]. Seven studies were specific to IC/BPS—5 RCT and 2 NRS combined for a total of 374 patients (3% men) with variations in BoNT-A isoforms [36–38, 42, 43, 46]. Forest plot for pain scores showed that, while half of the studies reported benefits, this did not achieve statistical significance.

BoNT-A for Bladder Pain Associated with Myofascial Pain CPPS

Myofascial pelvic pain (MPP), in which hypertonic pelvic floor muscles lead to chronic pain, is a significant cofactor in IC/BPS patients and may be the predominant etiology of pain in a majority of cases [49]. In addition to the negative impact MPP has on gynecological, sexual, and bowel function, urinary symptoms including bladder pain are also associated with myofascial pelvic pain [50]. Besides physical exam findings of hypertonicity and tenderness upon palpation, MPP can be objectively diagnosed by vaginal manometry with an elevated resting pressure of > 40 cm H_20. Treatment, like IC/BPS, is multidisciplinary and includes behavioral modifications, oral medications, pelvic floor–directed physical therapy, and trigger point injections (TPI) in refractory cases [9]. Approaches to TPI are varied, including transvaginal, transperineal, or paravaginal/subgluteal but with common targets of the iliococcygeus, pubococcygeus, puborectalis, coccygeus, obturator internus, and superficial and deep transverse perineii [51]. Various pharmacological agents have been used in TPI including local anesthetics, steroids, or BoNT-A.

BoNT-A was first shown to be effective as an adjunctive agent via TPI by Jarvis et al. in 2004. All twelve subjects treated with 40 IU reported improved pain and sexual function at 3 months post-injection of BoNT-A in the pubococcygeus and puborectalis [52].

In more contemporary literature, Adelowo et al. [54•] performed a retrospective cohort study of 31 patients who underwent TPI with 100–300 IU of BoNT-A. Baseline demographics showed 89.7% of women with severe levator pain upon palpation, 92.3% with dyspareunia, and 62.1% with urinary urgency. After 6 weeks, mean pain score was 3 compared to a baseline of 9.5 ($p < 0.0001$). Complications included higher post void residual (SMD 16.5 ml, $p = 0.56$), urinary retention (22%, $p = 0.38$), urinary incontinence (11.1%, $p = 0.03$), and fecal incontinence (5.6%). Similarly, Halder et al. [55] reported a significant reduction in pain (3.7 ± 4.0 vs 6.4 ± 1.8, $p = 0.005$) at 8 weeks in a retrospective study of patients ($n = 50$) who underwent physical therapy plus TPI with 200 IU of BoNT-A.

Conversely, in a RCT of 60 patients to either 200 IU of Botox or normal saline along with 8 weeks of pelvic floor physical therapy, Dessie et al. [56] reported that the treatment group reported a greater reduction in VAS, but this was not significant ($p = 0.16$). Moreover, though scores on the Pelvic Floor Distress Inventory (PFDI) were improved at 2 weeks ($p = 0.01$) in patients receiving BoNT-A, this benefit did not persist at 4 ($p = 0.19$) or 6 weeks ($p = 0.11$). Most common adverse effect was urinary incontinence (22%) and constipation (10.1%). This was again seen when Abbott and colleagues [53] randomized 60 women to either 80 IU of BoNT-A ($n = 30$) or normal saline ($n = 30$). Changes in VAS scores, EuroOOL-5D (EQ-5D), Short-Form 12 Health Survey (SF-12), Sexual Activity Questionnaire, and vaginal manometry were measured. At 6 months, the BoNT-A group had significantly less dyspareunia ($p < 0.001$) and non-menstrual pelvic pain ($p < 0.001$) from baseline. However, intergroup differences were insignificant when compared to the placebo group as they also reported a decrease in dyspareunia ($p = 0.043$) from baseline. Vaginal manometry measurements showed decreases in resting pressures in both the BoNT-A group (49 vs 32, $p < 0.001$) and the placebo group (44 vs 39, $p = 0.003$).

Parsons' systematic review included 4 studies—3 RCT, 1 NRS—on gynecological pain with a combined cohort of 194

Table 1 Study design and outcome measures

Study (year)	Intervention Dose, site, number of injections	N	Endpoint	Outcomes			
				VAS	GRA	OLS/CPSI-F	CBC (ml)
Kuo (2009)		67	3 m				
	HD (IVP 80 cmH_2O, 15 min)	23		4.30 ± 2.6 to 3.52 ± 3.07	48%	12.8 ± 3.41 to 9.87 ± 4.85	280 ± 100.8 to 292 ± 99.5
	HD + 100 IU ONA, trigone sparing, 40 sites	29		4.83 ± 2.21 to 2.97 ± 1.99	72%	12.5 ± 2.15 to 8.17 ± 4.06	308.5 ± 135 to 388 ± 126.8
	HD + 200 IU ONA, trigone sparing, 40 sites	15		5.47 ± 2.1 to 2.47 ± 2.1	80%	13.9 ± 2.53 to 8.9 ± 5.58	250.5 ± 86.7 to 406.9 ± 178.9
	p value			0.007	0.032	NS	NS
Gottsch (2011)		20	3 m				
	Saline injection, periurethral, 2 sites	11		NR	NR	29.6 to 27.7	NR
	50 IU ONA, periurethral, 2 sites	9		-0.3	NR	35.2 to 31.3	NR
	p value			NR	NR	0.97	NR
Kasyan (2012)		32	3 m				
	HD	15		8.7 ± 1.2 to 6.1 ± 2.8	NR	14.5 ± 2. to 9.4 ± 2.9	NR
	100 IU BoNT-A (type NR), trigone, number of injections NR	17		9.3 ± 0.9 to 5.8 ± 2.4	NR	13.8 ± 3.7 to 8.8 ± 3.3	NR
	p value			$p > 0.05$	NR	$p > 0.05$	NR
Lee (2013)		40	24 m				
	100 IU BoNT-A every 6 m, trigone sparing, 40 sites, with Hunner's lesions	10		NR	1	NR	-13
	100 IU BoNT-A every 6 m, trigone sparing, 40 sites, without Hunner's lesions, GRA ≥ 2	15		NR	-2	NR	-69
	100 IU BoNT-A every 6 m, trigone sparing, 40 sites, without Hunner's lesions, GRA < 2	15		NR	-1	NR	-64
Study (year)	Intervention Dose, site, number of injections	N	Endpoint	Outcomes			
				VAS	GRA	OLS/CPSI-F	CBC (ml)
Manning (2014)		53	3 m				
	HD + Saline injection, trigone sparing, 30 sites	27		NR	NR	1.5 vs, $p = 0.12$	-18 cc
	HD + 500 IU ABO, trigone sparing, 30 sites	26		NR	NR	3.7	19.66
	p value			NR	NR	$p = 0.12$	0.27
Lee (2015)		104					

Table 1 (continued)

Study (year)	Intervention Dose, site, number of injections	N	Endpoint	Outcomes			
				VAS	GRA	OLS/CPSI-F	CBC (ml)
	HD + 100 IU ONA, site NR, number of injections sites NR	104	24 m	5.2 ± 2.4 at 0 m, 3.5 ± 2.5 at 6 m, 2.9 ± 2.3 at 24 m,	0 at 0 m, 1.3 ± 0.97 at 6 m, 1.8 ± 1.1 at 24 m	23.7 ± 6.1 at 0 m, 16.6 ± 8.9 at 6 m, 15.2 ± 8.9 at 24 m,	129.1 ± 75.0 ml at 0 m, 177.7 ± 85.0 ml at 6 m, 345.2 ± 149.4 ml at 24 m
	p value			p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
Gao (2015)		124	12 m				
	HD + Sodium hyaluronate instillation weekly for 1 m, then monthly for 5 months	58		9.2 ± 0.8 to 7.9 ± 1.3	NR	34.7 ± 1.5 to 34.2 ± 1.5	NR
	HD + 100 IU INCO, entire bladder, 20 sites	66		9.4 ± 0.9 to 8.1 ± 1.3	NR	34.2 ± 1.7 to 31.2 ± 2.4	NR
	p value			NR	NR	p < 0.05	NR
Kuo (2016)		32	2 m				
	HD + normal saline, trigone sparing, 20 sites	17		-0.9 ± 2.2	1.3 ± 1.4	5.8 ± 9	-45.4 ± 138.5
	HD + 100 IU ONA, trigone sparing, 20 sites	15		2.6 ± 2.8	1.5 ± 1.3	9.6 ± 7.5	67.8 ± 164.3
	p value			p = 0.021	P = 0.257	p = 0.11	p = 0.02
Pinto (2018)		21	3 m				
	Saline injection, site NR, 10 sites	10		–1.6 ± 2.1	NR	7.1 ± 4.6	NR
	100 IU ONA, site NR, 10 sites	11		–3.8 ± 2.5	NR	–9 ± 4.7	NR
	p value			< 0.05	NR	p < 0.05	NR
Study (year)	Intervention Dose, site, number of injections	N	Endpoint	Outcomes			
				VAS	GRA	OLS/CPSI-F	CBC (ml)
Jiang (2018)			2 m				
	HD + 100 IU ONA, trigone sparing, 20 sits	20		3.15 ± 2.18	1.35 ± 1.14	17.1 ± 8.87	284 ± 136 to 272 ± 147
	HD + 100 IU ONA, trigone only, 10 sites	19		2.68 ± 1.86	1.32 ± 1.06	14.1 ± 8.4	234 ± 130 to 320 ± 184
	p value			p = 0.82	p = 0.92	p = 0.96	0.11
Evans (2020)	100 IU BoNT-A, trigone only, 10 sites	12	3 m	NR	NR	13.8 to 10.5	NR
	100 IU BoNT-A, trigone sparing, 10 sites	14		NR	NR	14.93 to 12.9	NR
	p value					0.21	

**ONA* onabotulinum toxin A, *ABO* abobotulinum toxin A, *INCO* incobotulinum toxin A, *IU* international unit, *ml* milliliter, *m* month, *ICSI* interstitial cystitis symptom index, *ICPI* interstitial cystitis problem index, *OLS* O'Leary-Sant score (equal to ICSI + ICPI), *VAS* visual analogue scale, *GRA* global response assessment, *FBC* functional bladder capacity, *CBC* cystometric bladder capacity, *HD* hydrodistention, *NR* not recorded, *NS* not significant

patients. All studies evaluated ONA with dose ranging from 20 to 100 IU between 2 and 5 sites for diagnoses of vestibulodynia and pelvic floor myalgia. At 6 months, there were no differences in pain reduction between the two groups [48].

In our experience at Beaumont, we identified that BoNT-A plus standard TPI did not necessarily improve pain reduction [57]. In a RCT of 21 women who underwent TPI with triamcinolone plus local anesthetic and either 200 IU of BoNT-A or placebo (normal saline), we found no difference in median numerical rating scale pain scores at 1 month between groups steroid, 5 (range 3–8, $n=10$) vs. Botox, 4.5 (range 2–7, $n=9$); $p=0.82$. The change in median pain scores between 1 month and baseline was no different between groups—steroid, − 1 (range − 2 to + 3) vs. Botox, − 2 (range − 4 to 0) ($p=0.072$). Although not significant, 44%, 62.5%, and 44% of patients at 1, 3, and 6 months follow-up were moderately or markedly improved on the GRA in the BTX group compared to 10%, 25%, and 0%, respectively, in the steroid group. Both groups would recommend TPI at 3 and 6 months.

Future of Therapy and Limitations

An exciting area of research has been in using liposomes as a novel delivery mechanism of intracellular BoNT-A [27]. Liposomes are lipid vesicles with an aqueous core that allows delivery of pharmacological agents via cellular endocytosis. However, even empty liposomes can facilitate healing of the damage urothelium by coating the damaged mucosal lining in IC/BPS and reduce pain [58]. Chuang and associates [58] compared intravesical instillation of liposomes (80 mg/40 ml) to oral pentosan polysulfate sodium (100 mg) in 24 patients with IC/BPS and found that there was significant reductions in frequency, OLS and VAS scores, with no reported side effects. These findings were supported by Peters et al. in an open-label study of 14 IC/BPS patients who had liposomal instillations weekly for 4 weeks. Pain ($p=0.01$) and urgency ($p=-0.084$) were all reduced at 3 months, again without any adverse effects [59]. Following that, Kuo et al. [60] conducted a single-center double-blinded RCT of liposomal BoNT-A (lipo-BoNT) in 24 overactive bladder patients. At 1 month, the primary outcome of frequency was significantly improved in the experimental group ($n=12$, $p=0.008$) compared to the placebo ($n=12$, $p=0.79$), as was urgency ($p=0.01$ vs 0.2).

The first multi-centered RCT of lipo-BoNT by Chuang [61•] in 2014 enrolled overactive bladder patients refractory to medical therapy. Fifty-five patients were enrolled and randomized to either lipo-BoNT ($n=28$) or normal saline ($n=27$) bladder instillation. At 1 month, lipo-BoNT group had significantly lower number of daily voids (− 4.6 vs − 0.2, $p=0.036$) and urgency (− 7.43) though the latter was not significant. No adverse events were reported including urinary tract infections or urinary retention. It is worth noting that there is one current RCT evaluating the role of lipo-BoNT in treating IC/BPS with pending publication [62].

Conclusion

Contemporary literature suggests that intradetrusor injection of BoNT-A may provide pain reduction in patients with IC/BPS though it may not improve functional outcome measures, such as bladder capacity. Whether delivered via trigone or as trigone-sparing does not impact efficacy; however, the presence of Hunner's lesions may forbode a lower pain reduction. With regard to CPPS, current study findings suggest that TPI combined with BoNT-A may not live up to the anticipated promise addressing pain associated with hypertonic pelvic floor muscles. This finding is in line with our experience. However, variations in dosage and limited number of randomized controlled studies may be a factor. Further well-designed randomized studies are needed to elucidate the true role BoNT-A plays in managing pelvic pain. It is possible that addressing hypertonicity alone may not be sufficient, as chronic pain is likely mediated through multiple mechanisms. The future therapy of liposomal BoNT appears to be promising and results are highly anticipated.

Declarations

Conflict of Interest The authors declare no competing interests.

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.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Hanno PM, Erickson D, Moldwin R, Faraday MM, Association AU. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol. 2015;193(5):1545–53. https://doi.org/10.1016/j.juro.2015.01.086.
2. Suskind AM, Berry SH, Ewing BA, Elliott MN, Suttorp MJ, Clemens JQ. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: results of the RAND Interstitial Cystitis Epidemiology male study. J Urol. 2013;189(1):141–5. https://doi.org/10.1016/j.juro.2012.08.088.

3. Warren JW, Howard FM, Cross RK, et al. Antecedent non-bladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. Urology. 2009;73(1):52–7. https://doi.org/10.1016/j.urology.2008.06.031.
4. Talati A, Ponniah K, Strug LJ, Hodge SE, Fyer AJ, Weissman MM. Panic disorder, social anxiety disorder, and a possible medical syndrome previously linked to chromosome 13. Biol Psychiatry. 2008;63(6):594–601. https://doi.org/10.1016/j.biopsych.2007.07.021.
5. Ahangari A. Prevalence of chronic pelvic pain among women: an updated review. Pain Physician. 2014;17(2):E141-7.
6. Latthe P, Mignini L, Gray R, Hills R, Khan K. Factors predisposing women to chronic pelvic pain: systematic review. BMJ. 2006;332(7544):749–55. https://doi.org/10.1136/bmj.38748.697465.55.
7. Purwar B, Khullar V. Use of botulinum toxin for chronic pelvic pain. Womens Health (Lond). 2016;12(3):293–6. https://doi.org/10.2217/whe-2016-0007.
8. Hanno PM, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2011;185(6):2162–70. https://doi.org/10.1016/j.juro.2011.03.064.
9. Fall M, Baranowski AP, Elneil S, et al. EAU guidelines on chronic pelvic pain. Eur Urol. 2010;57(1):35–48. https://doi.org/10.1016/j.eururo.2009.08.020.
10. Scaglione F. 2016 Conversion Ratio between Botox®, Dysport®, and Xeomin® in Clinical Practice. *Toxins (Basel)* 8(3) https://doi.org/10.3390/toxins8030065
11. Dolly JO, O'Connell MA. Neurotherapeutics to inhibit exocytosis from sensory neurons for the control of chronic pain. Curr Opin Pharmacol. 2012;12(1):100–8. https://doi.org/10.1016/j.coph.2011.11.001.
12. Rummel A. The long journey of botulinum neurotoxins into the synapse. Toxicon. 2015;107(Pt A):9–24. https://doi.org/10.1016/j.toxicon.2015.09.009.
13. Antonucci F, Corradini I, Fossati G, Tomasoni R, Menna E, Matteoli M. SNAP-25, a Known Presynaptic Protein with Emerging Postsynaptic Functions. Front Synaptic Neurosci. 2016;8:7. https://doi.org/10.3389/fnsyn.2016.00007.
14. Bleakman D, Alt A, Nisenbaum ES. Glutamate receptors and pain. Semin Cell Dev Biol. 2006;17(5):592–604. https://doi.org/10.1016/j.semcdb.2006.10.008.
15. Lucioni A, Bales GT, Lotan TL, McGehee DS, Cook SP, Rapp DE. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. BJU Int. 2008;101(3):366–70. https://doi.org/10.1111/j.1464-410X.2007.07312.x.
16. Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. Neurotoxicology. 2005;26(5):785–93. https://doi.org/10.1016/j.neuro.2005.01.017.
17. Bittencourt da Silva L, Karshenas A, Bach FW, Rasmussen S, Arendt-Nielsen L, Gazerani P. Blockade of glutamate release by botulinum neurotoxin type A in humans: a dermal microdialysis study. Pain Res Manag. 2014;19(3):126–32. https://doi.org/10.1155/2014/410415.
18. Burnstock G. Purinergic signalling in the urinary tract in health and disease. Purinergic Signal. 2014;10(1):103–55. https://doi.org/10.1007/s11302-013-9395-y.
19. Hanna-Mitchell AT, Wolf-Johnston AS, Barrick SR, et al. Effect of botulinum toxin A on urothelial-release of ATP and expression of SNARE targets within the urothelium. Neurourol Urodyn. 2015;34(1):79–84. https://doi.org/10.1002/nau.22508.
20. Khera M, Somogyi GT, Kiss S, Boone TB, Smith CP. Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. Neurochem Int. 2004;45(7):987–93. https://doi.org/10.1016/j.neuint.2004.06.001.
21. Apostolidis A, Popat R, Yiangou Y, et al. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol. 2005;174(3):977–82. https://doi.org/10.1097/01.ju.0000169481.42259.54 (**discussion 982-3**).
22. Schulte-Baukloh H, Priefert J, Knispel HH, Lawrence GW, Miller K, Neuhaus J. Botulinum toxin A detrusor injections reduce postsynaptic muscular M2, M3, P2X2, and P2X3 receptors in children and adolescents who have neurogenic detrusor overactivity: a single-blind study. Urology. 2013;81(5):1052–7. https://doi.org/10.1016/j.urology.2012.12.021.
23. Chuang YC, Yoshimura N, Huang CC, Wu M, Chiang PH, Chancellor MB. Intravesical botulinum toxin A administration inhibits COX-2 and EP4 expression and suppresses bladder hyperactivity in cyclophosphamide-induced cystitis in rats. Eur Urol. 2009;56(1):159–66. https://doi.org/10.1016/j.eururo.2008.05.007.
24. Shie JH, Liu HT, Wang YS, Kuo HC. Immunohistochemical evidence suggests repeated intravesical application of botulinum toxin A injections may improve treatment efficacy of interstitial cystitis/bladder pain syndrome. BJU Int. 2013;111(4):638–46. https://doi.org/10.1111/j.1464-410X.2012.11466.x.
25. Peck MW, Smith TJ, Anniballi F, et al. Historical Perspectives and Guidelines for Botulinum Neurotoxin Subtype Nomenclature. *Toxins (Basel)*. 2017;9(1)https://doi.org/10.3390/toxins9010038
26. Chen CL, Meng E. Can Botulinum Toxin A Play A Role In Treatment Of Chronic Pelvic Pain Syndrome In Female Patients?-Clinical and Animal Evidence. *Toxins (Basel)*. 2020;12(2)https://doi.org/10.3390/toxins12020110
27. Janicki JJ, Chancellor MB, Kaufman J, Gruber MA, Chancellor DD. Potential effect of liposomes and liposome-encapsulated botulinum toxin and tacrolimus in the treatment of bladder dysfunction. *Toxins (Basel)*. 2016;8(3)https://doi.org/10.3390/toxins8030081
28. Atassi MZ. Basic immunological aspects of botulinum toxin therapy. Mov Disord. 2004;19(Suppl 8):S68-84. https://doi.org/10.1002/mds.20020.
29. Kazerooni R, Broadhead C. Cost-utility analysis of botulinum toxin type A products for the treatment of cervical dystonia. Am J Health Syst Pharm. 2015;72(4):301–7. https://doi.org/10.2146/ajhp140276.
30. Scott AB, Rosenbaum A, Collins CC. Pharmacologic weakening of extraocular muscles. Invest Ophthalmol. 1973;12(12):924–7.
31. Dykstra DD, Sidi AA, Scott AB, Pagel JM, Goldish GD. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. J Urol. 1988;139(5):919–22. https://doi.org/10.1016/s0022-5347(17)42717-0.
32. Ginsberg D, Gousse A, Keppenne V, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol. 2012;187(6):2131–9. https://doi.org/10.1016/j.juro.2012.01.125.
33. Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2011;60(4):742–50. https://doi.org/10.1016/j.eururo.2011.07.002.
34. Nitti VW, Dmochowski R, Herschorn S, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo

controlled trial. J Urol. 2013;189(6):2186–93. https://doi.org/10.1016/j.juro.2012.12.022.
35. Chapple C, Sievert KD, MacDiarmid S, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2013;64(2):249–56. https://doi.org/10.1016/j.eururo.2013.04.001.
36. Kuo HC, Chancellor MB. Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int. 2009;104(5):657–61. https://doi.org/10.1111/j.1464-410X.2009.08495.x.
37. G K. Randomized controlled trial for efficacy of botulinum toxin type a in treatment of patients suffering bladder pain syndrome/interstitial cystitis with Hunner's lesions: preliminary results. *Journal of Urology*. 2012;187:335–6.
38. Manning J, Dwyer P, Rosamilia A, Colyvas K, Murray C, Fitzgerald E. A multicentre, prospective, randomised, double-blind study to measure the treatment effectiveness of abobotulinum A (AboBTXA) among women with refractory interstitial cystitis/bladder pain syndrome. Int Urogynecol J. 2014;25(5):593–9. https://doi.org/10.1007/s00192-013-2267-8.
39. Gottsch HP, Miller JL, Yang CC, Berger RE. A pilot study of botulinum toxin for interstitial cystitis/painful bladder syndrome. Neurourol Urodyn. 2011;30(1):93–6. https://doi.org/10.1002/nau.20946.
40. Kuo HC, Jiang YH, Tsai YC, Kuo YC. Intravesical botulinum toxin-A injections reduce bladder pain of interstitial cystitis/bladder pain syndrome refractory to conventional treatment - A prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial. Neurourol Urodyn. 2016;35(5):609–14. https://doi.org/10.1002/nau.22760.
41 Pinto RA, Costa D, Morgado A, et al. Intratrigonal OnabotulinumtoxinA Improves Bladder Symptoms and Quality of Life in Patients with Bladder Pain Syndrome/Interstitial Cystitis: A Pilot, Single Center, Randomized, Double-Blind, Placebo Controlled Trial. J Urol. 2018;199(4):998–1003. https://doi.org/10.1016/j.juro.2017.10.018.
42. Lee CL, Kuo HC. Intravesical botulinum toxin a injections do not benefit patients with ulcer type interstitial cystitis. Pain Physician. 2013;16(2):109–16.
43. Evans RJ, Overholt T, Colaco M, Walker SJ. Injection location does not impact botulinum toxin A efficacy in interstitial cystitis/bladder pain syndrome patients. Can J Urol. 2020;27(1):10125–9.
44 Jiang YH, Jhang JF, Lee CL, Kuo HC. Comparative study of efficacy and safety between bladder body and trigonal intravesical onabotulinumtoxina injection in the treatment of interstitial cystitis refractory to conventional treatment-A prospective, randomized, clinical trial. Neurourol Urodyn. 2018;37(4):1467–73. https://doi.org/10.1002/nau.23475.
45.• Lee CL, Kuo HC. Long-Term Efficacy and Safety of Repeated Intravescial OnabotulinumtoxinA Injections Plus Hydrodistention in the Treatment of Interstitial Cystitis/Bladder Pain Syndrome. Toxins (Basel). 2015;7(10):4283–93. https://doi.org/10.3390/toxins7104283. (**This prospective study is the only one to report sustained long-term effectiveness of BoNT-A injections in reducing pain and improving bladder capacity.**)
46. Gao Y, Liao L. Intravesical injection of botulinum toxin A for treatment of interstitial cystitis/bladder pain syndrome: 10 years of experience at a single center in China. Int Urogynecol J. 2015;26(7):1021–6. https://doi.org/10.1007/s00192-015-2631-y.
47. Shim SR, Cho YJ, Shin IS, Kim JH. Efficacy and safety of botulinum toxin injection for interstitial cystitis/bladder pain syndrome: a systematic review and meta-analysis. Int Urol Nephrol. 2016;48(8):1215–27. https://doi.org/10.1007/s11255-016-1295-y.
48 Parsons BA, Goonewardene S, Dabestani S, et al. The benefits and harms of botulinum toxin-A in the treatment of chronic pelvic pain syndromes: a systematic review by the European Association of Urology Chronic Pelvic Pain Panel. Eur Urol Focus. 2021. https://doi.org/10.1016/j.euf.2021.01.005.
49. Mathias SD, Kuppermann M, Liberman RF, Lipschutz RC, Steege JF. Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. Obstet Gynecol. 1996;87(3):321–7. https://doi.org/10.1016/0029-7844(95)00458-0.
50. Srinivasan AK, Kaye JD, Moldwin R. Myofascial dysfunction associated with chronic pelvic floor pain: management strategies. Curr Pain Headache Rep. 2007;11(5):359–64. https://doi.org/10.1007/s11916-007-0218-0.
51. Moldwin RM, Fariello JY. Myofascial trigger points of the pelvic floor: associations with urological pain syndromes and treatment strategies including injection therapy. Curr Urol Rep. 2013;14(5):409–17. https://doi.org/10.1007/s11934-013-0360-7.
52. Jarvis SK, Abbott JA, Lenart MB, Steensma A, Vancaillie TG. Pilot study of botulinum toxin type A in the treatment of chronic pelvic pain associated with spasm of the levator ani muscles. Aust N Z J Obstet Gynaecol. 2004;44(1):46–50. https://doi.org/10.1111/j.1479-828X.2004.00163.x.
53. Abbott JA, Jarvis SK, Lyons SD, Thomson A, Vancaille TG. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. Obstet Gynecol. 2006;108(4):915–23. https://doi.org/10.1097/01.AOG.0000237100.29870.cc.
54.• Adelowo A, Hacker MR, Shapiro A, Modest AM, Elkadry E. Botulinum toxin type A (BOTOX) for refractory myofascial pelvic pain. Female Pelvic Med Reconstr Surg. 2013;19(5):288–92. https://doi.org/10.1097/SPV.0b013e3182989fd8. (**Authors demonstrated that BoNT-A with TPI can reduce pelvic pain though there are temporary adverse effects.**)
55. Halder GE, Scott L, Wyman A, et al. Botox combined with myofascial release physical therapy as a treatment for myofascial pelvic pain. Investig Clin Urol. 2017;58(2):134–9. https://doi.org/10.4111/icu.2017.58.2.134.
56 Dessie SG, Von Bargen E, Hacker MR, Haviland MJ, Elkadry E. A randomized, double-blind, placebo-controlled trial of onabotulinumtoxin A trigger point injections for myofascial pelvic pain. Am J Obstet Gynecol. 2019;221(5):517.e1-517.e9. https://doi.org/10.1016/j.ajog.2019.06.044.
57. Bartley J, Nguyen L, Hasenau D, et al. 2019 PD20–09 Onobotuliumtoxin A versus Kenalog for intravaginal trigger point injections in the treatment of chronic pelvic pain. https://doi.org/10.1097/01.JU.0000555741.75359.15
58. Chuang YC, Lee WC, Chiang PH. Intravesical liposome versus oral pentosan polysulfate for interstitial cystitis/painful bladder syndrome. J Urol. 2009;182(4):1393–400. https://doi.org/10.1016/j.juro.2009.06.024.
59. Peters KM, Hasenau D, Killinger KA, Chancellor MB, Anthony M, Kaufman J. Liposomal bladder instillations for IC/BPS: an open-label clinical evaluation. Int Urol Nephrol. 2014;46(12):2291–5. https://doi.org/10.1007/s11255-014-0828-5.
60. Kuo HC, Liu HT, Chuang YC, Birder LA, Chancellor MB. Pilot study of liposome-encapsulated onabotulinumtoxina for

patients with overactive bladder: a single-center study. Eur Urol. 2014;65(6):1117–24. https://doi.org/10.1016/j.eururo.2014.01.036.

61.• Chuang YC, Kaufmann JH, Chancellor DD, Chancellor MB, Kuo HC. Bladder instillation of liposome encapsulated onabotulinumtoxina improves overactive bladder symptoms: a prospective, multicenter, double-blind, randomized trial. J Urol. 2014;192(6):1743–9. https://doi.org/10.1016/j.juro.2014.07.008. (**This well-designed multi-centered RCT of lipo-BoNT in refractory OAB patients is an exciting as it promises the next technological advancement for intravesical BoNT-A. Patient's frequency improved while suffering from no side effects that commonly plagues BoNT-A injections. If results in larger trials continue to show efficacy, the role of lipo-BoNT may surpass that of BoNT-A injections.**)

62. Kuo H-C. https://clinicaltrials.gov/ct2/show/NCT02247557.