Clinical Application of Botulinum Toxin A for Interstitial Cystitis/Painful Bladder Syndrome

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ABSTRACT

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a debilitating chronic disease of unknown etiology characterized by urgency frequency and suprapubic pain at full bladder. Various therapy options including oral pentosan polysulphate, cyclosporine A, amitriptyline, and intravesical heparin, hyaluronic acid, bacilli Calmette Guerin, resiniferatoxin have not demonstrated long-term effects. Intravesical injection of botulinum toxin A (BoNT-A) has been introduced to treat IC/PBS although its use in lower urinary tract dysfunction remains unlicensed. Small scale studies suggested the short term efficacy of a single injection of BoNT-A seemed promising with acceptable adverse events. However, the long term effects of repeated BoNT-A injection need to be elucidated. In addition, the method of administration (i.e. dose, volume and site of injection) still requires further determination.

Key words: painful bladder syndrome, botulinum toxin, treatment

INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a debilitating chronic disease of unknown etiology characterized by urgency frequency and suprapubic pain at full bladder. Current treatments are usually unsuccessful in completely eradicating bladder pain and increasing bladder capacity [1]. Intravesical resiniferatoxin was once considered effective but this was not shown in a large-scaled, multiple center trial [2]. Other intravesical therapies such as hyaluronic acid, bacilli Calmette Guerin, and oral medications with pentosan polysulphate, cyclosporine A, and amitriptyline have not demonstrated long-term effectiveness [3-6]. Bladder hydrodistention is still the most popular treatment for IC/PBS refractory to conventional treatment. However, the effective duration of hydrodistention is usually short and repeated hydrodistention or conversion to other treatments is necessary.

The unreliable effective therapy for IC/PBS is possibly a result of poorly understood pathophysiology. One of the most common findings in bladder mucosal biopsies from IC/PBS patients is denudation or thinning of the bladder epithelium, suggesting altered regulation of urothelial homeostasis. Other bladder abnormalities include increased nerve fiber density and inflammatory cell infiltration. Although investigations have been enthusiastically perfomed, the etiology of IC/PBS remains unknown. A recent Interstitial Cystitis Data Base study noted that loss of epithelial integrity is a predominant histopathologic finding. The epithelial damage may precede the other histopathologic findings in the bladder wall. The suburothelial space immediately below the basal lamina is well supplied with sensory nerves which transmit the sensation of bladder fullness and response to bladder inflammation [7,8]. A local inflammatory process might be induced through the afferent and efferent nerves in the suburothelial interstitial cellular network which integrate the transmission of signals from the urothelium to the detrusor muscles in the bladder wall [9].

In a rat chemical cystitis model, a detrusor injection of botulinum toxin type A (BoNT-A) increased bladder capacity and compliance [10]. In other basic research, BoNT-A inhibited release of acetyl choline, norepinephrine, nerve growth factor, adenosine-5'-triphosphate, substance P and calcitonin gene-related peptide from the nerve fibers and urothelium [11-14]. Moreover, in a recent study using a cyclophosphamide induced cystitis model, Chuang et al demonstrated that intravesical BoNT-A administration could inhibit cyclooxygenase 2, and EP4 expression and suppress bladder hyperactivity in rats [15]. In clinical experiments, BoNT-A has been shown to reduce detrusor overactivity, impair bladder sensation, and decrease visceral pain in chronic inflammatory diseases [16-18]. These results suggest that BoNT-A treatment can modulate sensory and motor transmission, as well as reduce bladder inflammatory conditions. In this regard, inhibition of neuroplasticity of the sensory fibers in the suburothelial space by intravesical BoNT-A injections might have good therapeutic targeting for pain and sensory urgency in patients with IC/PBS [19].

BOTULINUM TOXIN FOR TREATMENT OF LOWER URINARY TRACT DISEASE

In 1988, Dysktra et al first published on the use of BoNT-A, injected into the external urinary sphincter, to treat detrusor sphincter dyssynergia in patients with spinal cord injury [20]. This was followed by Schurch et al using local injections of BoNT-A to treat neurogenic detrusor overactivity [21]. The applications list for lower urinary tract dysfunction (LUTD) has since increased to include idiopathic detrusor overactivity [22], bladder outflow obstruction [23], and IC/PBS [24].

Botulinum toxin (BoNT) use for LUTD remains unlicensed. There are seven serotypes of the toxin, BoNT-A to BoNT-G, with BoNT-A the most commonly used. The toxins disrupt different parts of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex, with BoNT-A acting against synaptosomal-associated protein-molecular weight 25 kDa (SNAP-25) [25]. Because SNAP-25 is necessary for fusion of neurotransmitter-filled vesicles with the plasma membrane and their release during exocytosis, its cleavage by BoNT-A causes a highly specific neuromuscular blockade of vesicular acetylcholine release at

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somatic and autonomic presynaptic nerve terminals [25]. Previously, internalisation of the neurotoxic component of BoNT-A has been achieved due to binding of the toxin to its specific receptor protein, synaptic vesicle protein 2 (SV2), in the presynaptic nerve terminals [25,26]. Both SNAP-25 and SV2 have been identified on nerve fibres in both the detrusor and suburothelium of human bladders [26,27]. The action of BoNT-A is not permanent because neuronal death does not occur and eventually the toxin is inactivated and removed.

BoNT-A was the first licensed serotype in clinical use under the trade name Botox (Allergan Pharmaceuticals, Irvine, CA, USA), however, other brands also exist , including Dysport (Ipsen Biopharm Ltd, Slough, UK), Xeomin (Merz Pharmaceuticals UK Ltd, Herts, UK), Prosigne (Lanzhou Biological Products, Lanzhou, China), and PurTox (Mentor Corporation, Madison, WI, USA). The different companies manufacturing BoNT-A have different isolation, extraction, purification, and formulation processes, and therefore different fragments of BoNT are isolated. Although the BoNT-A products are of the same serotype, their dose, efficacy, duration of effect, and safety profile are different enough for them not to be considered generic equivalents [28]. There are no randomised studies directly comparing the different agents for dose, efficacy, and safety for different indications. Consequently, it can be problematic to assume a direct dose correlation. However, it was said 1 U of Botox has been shown, in small studies, to be approximately similar in terms of efficacy to 3-5 U of Dysport [27,29,30], 1 U of Xeomin [31], and 1 U of Prosigne [32]. No BoNT preparations are licensed for use for any urologic application; therefore, it is essential that patients are informed of the correct evidence and risks prior to being given a specific BoNT preparation.

New terminology has been approved for different BoNT-A preparations. Botox is called onabotulinumtoxinA, Dysport is called abobotulinumtoxinA, and Xeomin is called incobotulinumtoxinA. The changes in the established drug names, enforced by the US Food and Drug Administration, were made to reinforce individual potencies, prevent drug errors, and to prevent interchangeability of products. At present, only onabotulinumtoxinA has been used for treatment of IC/PBS. We will try to assess the reported efficacy of onabotulinumtoxinA for the treatment of IC/PBS in adults and to document the reported details on the administration and adverse events of onabotulinumtoxinA.

BOTULINUM TOXIN FOR TREATMENT OF INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME

Assessment of results

Data were compiled into high-level data (level 1 and 2) and lower-level data (level 3). The levels of evidence chosen were those applied by the European Association of Urology [33]. Level 1 studies included randomised controlled studies, and level 2 studies included well-designed quasi-experimental studies. Level 3 studies included nonexperimental, comparative, and correlation studies. The most commonly reported outcome parameters, administration details, and adverse events from all of the studies were summarised and presented, giving due preference to high-level studies.

Statistical analysis

Where possible, the individual study data were converted in to a "percentage change" format so that they would be comparable between studies. This was done by subtracting the baseline (pretreatment) value from the posttreatment value and dividing by the baseline value by 100. The mean and the standard error of the mean were calculated for each parameter for the studies reporting on onabotulinumtoxinA at different doses. Conclusion statements were provided from the collected literature regarding the strength of the available evidence for both preparations of BoNT-A.

Efficacy of BoNT-A in IC/PBS

Pilot studies reporting the efficacy of BoNT-A for treating IC/PBS since 2004 have revealed controversial results [34-36]. However, most recent studies support the effects of BoNT-A in patients with chronic IC/PBS (Table 1) [36-44]. All nine articles mentioned in Table 1 reporting the use of BoNT-A for PBS/IC utilised onabotulinumtoxinA. Of these, one study was level 1 and two were level 2. One of the level 2 studies compared 100 U or 200 U onabotulinumtoxinA with hydrodistension versus hydrodistension alone [38]. At 3 months, there was a significant decrease in symptom indices, symptoms recorded in a bladder diary, and urodynamic parameters with onabotulinumtoxinA compared with hydrodistension alone. The other level 2 study showed more improvement in frequency, nocturia, and global IC score with 300 U of onabotulinumtoxinA compared with instillation of bacillus Calmette-Guerin. The level 1 study reported on quality of life (QoL) outcomes utilising the Chronic Prostatitis Symptom Index (female modification) and American Urological Association indices as well as graded chronic pain and perceived stress scales and the visual analogue scale (VAS); outcomes were not found to be significantly different from a placebo [37]. The authors emphasized that adjustment of the administrated dose, dilution method and injection site may may need further refinement. In Table 2, we combined all data describing onabotulinumtoxinA injections.

Administration: technique, site, and volume of injection for IC/PBS

Different injection depths (i.e. superficial muscle versus suburothelial) and various injection sites (whole bladder, trigonal or periurethral) have been reported for application of BoNT-A. The rationales for different injection methods are listed in Table 3. All nine studies in Table 1 used suburothelial injections for the treatment of IC/PBS. Of these, four included the trigone and one injected around the bladder neck. The volume varied from 2 mL to 30 mL in 10-40 injection sites. The method of administration clearly requires further study.

Adverse events in IC/PBS

Gottsch et al injected 50 U of onabotulinumtoxinA in to the bladder neck and found no systemic or local complications [37]. In contrast, Kuo and Chancellor reported 2 of 15 patients had haematuria, 7 had dysuria, and 5 with a large post-void residual urine (PVR) after receiving 200 U of onabotulinumtoxinA [38]. It must also be noted that patients received hydrodistension with onabotulinumtoxinA, but the incidence of haematuria and large PVR was 0%, and 4% developed dysuria after hydrodistension alone.

Long-term efficacy

Although BoNT-A injection seems promising in treating symptoms of IC, long term results have not shown successful outcomes. Giannantoni et al reported a one-year follow-up of 15 IC/PBS patients receiving BoNT-A injection therapy [40]. Thirteen of these patients

Table 1. Data for the Use of Botulinum Toxin A in Interstitial Cystitis/Painful Bladder Syndrome

Study	n	Follow-up	Preparation; dose	No. of injection sites; volume	Daytime frequency, %Δ	Nocturia, %Δ	Functional bladder capacity, %Δ	MCC, %Δ	VAS, %Δ	QoL, %Δ	LOE
Gottsch et al [36]	9	3 mo	Botox; 50 U	2 mL	-	-	-	-	-	CPSI-F: -11	1
	11		Placebo	-	-	-	-	-	-	CPSI-F: -4	-
Kuo and Chancellor [37]	15	3 mo	Botox and hydrodistension; 200 U	40; 20 mL	-34	-51	40	62	-55	-	2
	29		Botox and hydrodistension; 100 U	-	-25	-24	17	26	-39	-	-
	23		Hydrodistension	-	-14	-5	9	4	-18	-	-
El-Bahnasy et al [38]	16	22 wk	BCG	-	-31	-54	-	-	-	GICS: -71	2
	16	23 wk	Botox; 300 U	-	-68	-100	-	-	-	GICS: -92	-
Giannantoni et al [35]	14	1 mo	Botox; 200 U	20; 20 mL	-41	-53	-	37	-38	-	3
Giannantoni et al [39]	15	1 mo	Botox; 200 U	20; 20 mL	-48	-67	-	41	-35	-	3
Giannantoni et al [40]	13	1 mo	Botox; 200 U	20; 20 mL	-50	-75	-	32	-36	-	3
Giannantoni et al [41]	14	3 mo	Botox; 200 U	20 mL	-56	-74	-	90	-46	SF-36, HAM-A, HAM-D	3
Pinto et al [42]	26	1 mo	Botox; 100 U	10; 10 mL	-52	-51	-	130	-64	-	3
Ramsay et al [43]	11	6 wk	Botox; 200-300 U	20-30; 20-30 mL	-	-	-	29	-	BFLUTS/ KHQ	3

BCG=bacillus Calmette-Guerin; CPSI-F=Chronic Prostatitis Symptom Index (female modification); GICS=Global Interstitial Cystitis Score; HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale; KHQ=King's Health Questionnaire; LOE=level of evidence; MCC=maximum cystometric capacity; QoL=quality of life; VAS=visual analogue scale

Table 2. Outcomes of All Studies of OnabotulinumtoxinA for the Treatment of Interstitial Cystitis/Painful Bladder Syndrome

Evidence	Levels of evidence	No. of studies; No. of patients	Daytime frequency, %Δ (SEM)	Nocturia, %Δ (SEM)	MCC, %Δ (SEM)	VAS, %Δ (SEM)
OnabotulinumtoxinA	1 and 2	3; 69	-42 (5)	-58 (13)	44 (18)	-47 (8)
OnabotulinumtoxinA	All	9; 162	-53 (3)	-70 (6)	60 (18)	-44 (6)

MCC=mean cystometric capacity; SEM=standard error of the mean; VAS=visual analogue scale

(86.6%) reported subjective improvement at the 1 and 3-month follow-ups. At 5 months, the beneficial effects persisted in 26.6% of cases, but frequency, nocturia and the pain VAS had increased. At 12 months, pain had recurred in all patients. Kuo et al demonstrated long term results with repeated BoNT-A injections every six months in 71 patients with refractory IC/PBS for up to 4 injections [45]. Among them, 71, 49, 32 and 19 patients completed one, two, three and four intravesical BoNT-A injections, respectively. As the number of treatments increased from one to four, the IC/PBS symptom score, pain VAS and daytime frequency significantly decreased. When the BoNT-A injection was repeated up to four times, functional bladder capacity, volume at full sensation and cystometric bladder capacity significantly increased. In addition, a successful result (change of Global Response Assessment scores ≥2) at 6 months after the first, second, third and fourth BoNT-A injection was reported in 24 (44%), 15 (44%), 9 (53%) and 7 (54%) patients. The overall incidences of adverse effects includ-

Table 3. Different Injection Depths and Sites of BoNT-A and Their Rationale for Treatment of Interstitial Cystitis/Painful Bladder Syndrome

Depths or sites	Rationales
Superficial muscle	Blockade of muscle contractility
Suburothelial	Blockade of afferent nerve and muscle contractility
Whole bladder	Blockade of afferent nerve and muscle contractility
Trigonal	Mostly blockade of afferent nerve without interference of muscle contractility
Periurethral	Blockade of urethral afferent signal that perpetuate the detrusor reflex

ing urinary tract infection, dysuria, intermittent catheterization, acute urine retention and hematuria during the first, second, third and fourth treatments were 28%, 29%, 45% and 32%, respectively.

CONCLUSIONS

In comparison with studies of BoNT-A for treatment of other LUTD, the studies of this drug for treatment of IC/PBS were relatively fewer, smaller scaled, and lower evidence-based level. Intravesical injection (with or without trigone involvement) of BoNT-A seems effective in reducing daily frequency, nocturia, and pain VAS, and improving functional bladder capacity, maximum cystometric capacity and QoL in IC/PBS patients in the short term. The long term efficacy of repeated BoNT-A for treatment of IC/PBS and the optimal administration method require further confirmation.

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