Repeated Intravesical Botulinum Toxin A Injections Plus Hydrodistention might be a Rational Treatment of Interstitial Cystitis Refractory to Conventional Treatment — A Hypothesis

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ABSTRACT

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a mysterious chronic disease of unknown etiology characterized by urgency frequency and suprapubic pain at full bladder. Most current treatments are not successful in eradicating bladder pain and increasing bladder capacity. Loss of epithelial barrier function is a predominant histopathologic finding in IC/PBS. 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. Botulinum toxin A (BoNT-A) treatment can modulate sensory transmission as well as reduce detrusor contractility. Although BoNT-A injection seems promising in treating symptoms of IC, long term results have not shown successful outcomes. In a recent study, we found that the clinical results of intravesical BoNT-A injection followed by hydrodistention were significantly better compared to hydrodistention alone in treatment of IC/PBS. However, most patients had symptom relapse in the long-term. We hypothesized that repeated intravesical BoNT-A injections plus hydrodistention might have the following effects: (1) inhibition of sensory nerve neurotransmitter release, (2) inhibition of acetylcholine release in the neuromuscular junctions of the detrusor, and (3) desensitization of chronic inflammation in the dorsal root ganglia of the central nervous system. Hydrodistention alone might have an additive effect on excitation of the sensory nerves in the suburothelium, and together, these effects might enhance the effect of BoNT-A on sensory receptors in the bladder wall. Repeated intravesical BoNT-A injections plus hydrodistention might have clinical effects which increase bladder capacity and provide long-term pain relief in patients with IC/PBS who have been refractory to conventional treatment.
Key words: botulinum toxin, IC/PBS, intravesical treatment

INTRODUCTION

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a debilitating chronic disease of unknown etiology. IC/PBS is characterized by urgency frequency and suprapubic pain at full bladder. Most current treatments are usually not successful in eradicating bladder pain and increasing bladder capacity [1]. Intravesical resiniferatoxin (RTX) has been considered to have an effect but this has not been shown in a large scale multiple center trial [2]. Other intravesical therapies such as hyaluronic acid, bacilli Calmette Guerin, and oral medications with pentosan polysulphate (PPS, Elmiron), cyclosporine A, or amitriptyline have not demonstrated long-term effectiveness [3-6]. Bladder hydrodistention remains the most popular treatment for IC/PBS, however, the effective duration of hydrodistention is usually short and repeat hydrodistention is necessary.

PATHOPHYSIOLOGY OF IC/PBS

The pathophysiology of IC/PBS is poorly understood, and therefore, there is no definite treatment. Urothelial dysfunction, neurogenic inflammation, mast cell activation and allergy have been documented as possible etiologies of IC/PBS [1]. One of the most common findings in bladder mucosal biopsies from IC/PBS patients is denudation or thinning of the bladder epithelium, suggesting an altered regulation of urothelial homeostasis in the bladder of patients with IC/PBS. Other bladder abnormalities include increased nerve fiber density and inflammatory cell infiltration. Although there have been many investigations of this disorder, the etiology of IC/PBS remains unknown.

A recent IC data base study reported that loss of epithelial integrity is a predominant histopathologic finding in IC/PBS. 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, detrusor injection of botulinum toxin A (BoNT-A) has been shown to have effects on increasing bladder capacity [10]. Inhibition of neuroplasticity of the sensory fibers in the suburothelial space by intravesical BoNT-A injections might have good therapeutic targeting on pain and sensory urgency in patients with IC/PBS [11].

THERAPEUTIC EFFECTS OF BONT-A ON IC/PBS

BoNT-A has been widely reported to have satisfactory results in the treatment of neurogenic and idiopathic detrusor overactivity (DO) [12,13]. However, there have only been a few studies using BoNT-A in the treatment of IC/PBS [14-17]. In recent research, BoNT-A has been shown to inhibit the release of not only acetylcholine and norepinephrine, but also nerve growth factor (NGF), adenosine triphosphate, substance P and calcitonin gene-related peptide from nerve fibers and the urothelium [17-20]. Clinically, BoNT-A has been shown to reduce DO, impair bladder sensation, and decrease visceral pain in chronic inflammatory diseases [14,21,22]. These results suggest that BoNT-A treatment can not only reduce detrusor contractility but also modulate sensory transmission. BoNT-A intravesical injection has been shown

effective in treating symptoms of IC/PBS. Giannantoni et al found 85.7% of patients had improvement at 3 months [18]. However, the therapeutic effect decreased to 26.6% by 5 months and there was no effect by 12 months [23]. This limited success is possibly due to inadequate distribution of BoNT-A in the bladder wall, an inadequate dose of BoNT-A, or lack of some promoting factors which enhance the therapeutic effect of BoNT-A.

In a recent study, we compared the therapeutic results of 100 U or 200 U intravesical BoNT-A plus hydrodistention with results from hydrodistention alone [24]. Patients with IC/PBS who had failed conventional treatment were enrolled, and received suburothelial injection of 200 U or 100 U of BoNT-A followed by cystoscopic hydrodistention 2 weeks later (BoNT-A group). The control group received the identical hydrodistention procedure without BoNT-A injection. All patients continued to receive pentosan polysulphate and analgesics as baseline medication. A bladder pain visual analogue scale (VAS), O'Leary-Sant symptom and problem indexes, the functional bladder capacity (FBC), a quality of life index and urodynamic parameters were measured at baseline and after treatment. The maximum bladder capacity during hydrodistention increased from 589 ± 182 mL to 714 ± 174 mL (p= 0.001), and from 646 ± 196 to 802 ± 228 mL (p=0.000) 2 weeks after injections of 200 U and 100 U BoNT-A, respectively. The symptom score decreased in all three groups, but the VAS decreased, and the FBC and cystometric bladder capacity increased only in the BoNT-A groups at 3 months. Thirty-one of the 44 patients in the BoNT-A group (70.5%) had a successful result at 6 months, but only 8 (34.8%) of the patients treated with hydrodistention (P<0.001) achieved this result. Successful results were reported in 24 (54.6%) and 13 (30.0%) patients in the BoNT-A groups at 12 and 24 months, respectively, but in only 6 (26.1%) and 4 (17.4%) of the controls (p=0.0023). This study demonstrated that intravesical injections of 100 U BoNT-A plus hydrodistention increased bladder capacity and provided long-term pain relief in patients with IC/PBS and that these effects were superior to those obtained with hydrodistention alone.

HYPOTHESIS OF MECHANISM OF ACTION

BoNT-A -induced inhibition of rapid afferent firing has been demonstrated by a reduction of fos-positive cells in the dorsal horn of formalin-challenged rat models [25]. Increased central c-fos expression has been demonstrated in animal models of neurogenic detrusor overactivity and chronic bladder inflammation [26]. NGF has been demonstrated to activate transient potential vanilloid receptor subfamily 1 on small afferent nerves, which can promote release of substance P and induce neurogenic inflammation. Reduction of NGF production could lead to inhibition of neurogenic inflammation and further peripheral desensitization [7]. In treatment of chronic interstitial cystitis, this effect might have an important role in reducing bladder pain. If we can inject BoNT-A into the suburothelium repeatedly, the neurogenic inflammation in the dorsal root ganglia or central nervous system (sacral cords in interstitial cystitis) might be eliminated gradually and the visceral pain can thus be relieved.

If we can perform repeated intravesical injections of BoNT-A plus hydrodistention, the clinical effects of increased bladder capacity and long-term pain relief might be expected in patients with IC/PBS who have been refractory to conventional treatment. Repeated intravesical BoNT-A injections plus hydrodistention might have the following effects: (1) inhibition of sensory nerve neurotransmitter release, (2) inhibition of acetylcholine release in the neuromuscular junctions of the detrusor, and (3) desensitization of chronic inflammation in the dorsal root ganglia of the central nervous system. After injecting BoNT-A into the suburothelium, both detrusor muscles and suburothelial nerves might be adequately affected. Hydrodistention alone might have an effect on excitation of the sensory nerves in the suburothelium. Put together, these effects might enhance the effects of BoNT-A on sensory receptors in the bladder wall. Combined intravesical BoNT-A with hydrodistention may yield an additive effect both on pain relief and increased bladder capacity.

BoNT-A has been demonstrated to have anti-inflammatory effects in a rat model of cystitis [13] and can reduce bladder NGF levels after injection in patients with IC/PBS, with satisfactory pain relief [27]. However, BoNT-A injection alone might not be adequate in achieving a long-term effect for these patients. Another important factor for success in patients receiving repeated BoNT-A and hydrodistention might be the continuing combined treatment with baseline medication. Urothelial dysfunction, suburothelial inflammation and neurogenic inflammation in the detrusor muscle might exist alone or in combination in IC/PBS. Thus, a good therapeutic result in IC/PBS might not be expected with a single therapeutic modality such as oral PPS treatment, cystoscopic hydrodistention, intravesical resiniferatoxin or BoNT-A injection. Combined therapeutic modalities, such as use of a surface protectant, an anti-inflammatory agent or a tricyclic antidepressant with BoNT-A injection and hydrodistention might improve the therapeutic outcome especially in the patients with IC/PBS and a small bladder capacity [28].

CONCLUSION

Currently, there is no satisfactory treatment for bladder hypersensitivity and IC/PBS. Although a leaky urothelium has been speculated to cause chronic inflammation of the bladder, intravesical heparin therapy or oral PPS cannot eradicate the bladder pain and intractable frequency in most patients with IC/PBS, suggesting restoration of epithelial function can only partially repair the pathophysiology but not the inflammatory or possible central sensitization pain process that characterizes IC/PBS. We hypothesize that repeated BoNT-A injections plus hydrodistention should be used for refractory IC/PBS. This novel treatment modality might have the clinical effects of increasing bladder capacity and providing long-term pain relief in patients with IC/PBS who have been refractory to conventional treatment.

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