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Prospective Evaluation

Intravesical OnabotulinumtoxinA Injections for Refractory Painful Bladder Syndrome

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Background: Bladder pain associated with interstitial cystitis and painful bladder syndrome (IC/PBS) is frequently excruciating and intractable. The use of onabotulinumtoxinA (BoNT-A) for relief of this type of bladder pain has not been well described.

Objectives: To evaluate the efficacy and safety of intravesical BoNT-A injection for treatment of IC/PBS refractory to conventional treatment.

Study Design: Prospective, non-randomized study.

Setting: A tertiary medical center in Taiwan.

Methods: Sixty-seven patients with characteristic IC/PBS were enrolled. Intravesical injection of 100U of BoNT-A immediately followed by cystoscopic hydrodistention under intravenous general anesthesia. Changes of the urodynamic parameters, O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI), visual analog score (VAS) for pain, functional bladder capacity, and global response assessment (GRA) were evaluated at baseline and 6 months after BoNT-A injection. Adverse events that occurred after this procedure were also assessed.

Results: Significant improvement was shown after intravesical injection of 100 U of BoNT-A. Baseline and 6 months after injection scores were: ICSI and ICPI (23.6 ± 5.9 versus 15.2 ± 8.5, $P = 0.000$), VAS (5.3 ± 2.2 versus 3.3 ± 2.4, $P = 0.000$), functional bladder capacity (136 ± 77.6 versus 180 ± 78.2, $P = 0.000$) and GRA (0.3 ± 0.8 versus 1.4 ± 1.0, $P = 0.000$).

Limitations: This study lacks a placebo control group so the placebo effect cannot be eliminated. This study also does not provide information about the efficacy of this treatment after 6 months.

Conclusion: Intravesical onabotulinumtoxinA injection appears to be a safe and effective therapeutic option for analgesia and increased bladder capacity for patients with IC/PBS.

Institutional Review: This study was approved by the Institutional Review Board of the Buddhist Tzu-chi General Hospital.

Key words: Botulinum toxin, interstitial cystitis/painful bladder syndrome, intravesical treatment, bladder pain

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The pathophysiology of interstitial cystitis/painful bladder syndrome (IC/PBS) has not been fully understood. Associated clinical features of IC/PBS included lower urinary tract symptoms such as frequency and urgency. This syndrome complex usually results in severe pain and an impaired quality of life for these patients. Current treatments are usually unsuccessful in

completely eradicating bladder pain and increasing bladder capacity (1).

It is known that the suburothelial space is well supplied with sensory nerves which transmit the sensation of bladder fullness and response to bladder inflammation (2,3). One hypothesis to explain the pathology of IC/PBS is that an initial insult, such as urinary tract infection or chemical irritation to the bladder occurs, exciting sensory nerves located in the bladder wall. This excitation triggers an inflammatory response, or neurogenic inflammation, which when induced releases the neuropeptide substance P, causing the release of mast–cell mediators, histamines, cytokines, cell and tissue damage, and fibrosis. These conditions result in nervous system neuroplasticity via C–fibers and pain beyond the bladder develops (4). In an animal model of chemical cystitis, detrusor injection of onabotulinumtoxinA (BoNT-A) has been shown to have effects on increasing bladder capacity and compliance (5). 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 (6).

BoNT-A is one of the most powerful neurotoxins to inhibit the release of neurotransmitters from nerve fibers and urothelium (7,8). Applications of BoNT-A for IC/PBS have been reported in only a few studies (9-12). BoNT-A has been shown to reduce bladder pain, impaired bladder sensation, and decrease chronic inflammation in the central nervous system in animal and human experiments (9-12). Although BoNT-A injection seems promising for treating symptoms of IC/PBS, limited data were available to evaluate outcomes after a single injection for refractory IC/PBS.

The purpose of this study was to evaluate the efficacy and safety of intravesical BoNT-A injections for the treatment of IC/PBS refractory to conventional treatment.

Methods

Patient Enrollment

Sixty-seven patients with IC/PBS who had failed conventional treatments were prospectively enrolled in this study from July 2007 through August 2010. A diagnosis of IC/PBS had been established based on characteristic symptoms and cystoscopic findings of glomerulation, petechia, mucosal fissure, or ulceration (13). All patients had been treated with at least one of these medications: oral pentosanpolysulphate, intravesical instillation of heparin, hyaluronic acid, or tricyclic antidepressant for more than one year, but the symptoms remained unchanged or had relapsed. They were investigated thoroughly on enrollment and were excluded if they did not meet the inclusion criteria of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (14).

Clinical Assessment

Patients were asked to record a 3-day voiding diary prior to treatment to record their bladder capacity and their episodes of urinary frequency and nocturia. The IC/PBS symptoms were assessed by the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) (15). The pain score was reported by self-assessment using a 10-point visual analog scale (VAS) system. A videourodynamic study and potassium chloride (KCl) sensitivity test were performed and patients were informed of the possible complications associated with BoNT-A injection, such as generalized muscle weakness, difficult urination, transient urinary retention, or urinary tract infections. Outcome measurements were the change of the sum of ICSI and ICPI (15), and VAS from baseline to 6 months after the BoNT-A injection.

The treatment outcome was also assessed using the global response assessment (GRA) (16). Patients were requested to rate their bladder symptoms compared to baseline on a 7-point centered scale from markedly (-3), moderately (-2) and slightly worse (-1), no change (0), to slightly improved (+1), moderately improved (+2), and markedly improved (+3). Patients with moderately and markedly improved results after treatment were considered to have a successful treatment outcome. Otherwise, the treatment was considered to have failed.

Videourodynamic study

A videourodynamic study was performed by standard procedures using a 6 Fr dual channel catheter and an 8 Fr rectal balloon catheter. Cystometric study was performed with warmed normal saline at a filling rate of 20 mL/min. All descriptions and terminology in this report were in accordance with the recommendations of the International Continence Society (17). After the videourodynamic study, a 40 mL KCl solution of 0.4 M was infused slowly into the bladder. The test was regarded as positive when a painful sensation (of ≥2 VAS score) or urgency sensation was elicited, compared to a normal saline infusion during the prior videourodynamic study (18).

This study was approved by the Institutional Review Board and ethics committee of the hospital. Each patient was informed about the study rationale and procedures, and written, informed consent was obtained before treatment.

Botulinum Toxin Injections and Follow-up

Patients were admitted for the treatment. They received an intravesical injection of 100 U of onabotulinumtoxinA followed by cystoscopic hydrodistention under intravenous general anesthesia in the operating room.

Each vial of onabotulinumtoxinA was diluted with 20 mL of normal saline; 40 suburothelial injections were made. The injection needle was inserted into the urothelium at the posterior and lateral walls of the bladder, using a 23-gauge needle and rigid, 22 Fr cystoscopic injection instrument. Cystoscopic hydrodistention was performed to an intravesical pressure of 80 cm water for 15 minutes and the maximal bladder capacity (MBC) under hydrodistention was recorded. After the BoNT-A injections, a 14 Fr urethral Foley catheter was placed for one day and patients were discharged the next day. Oral antibiotics were prescribed for 7 days.

The patients were followed up at an outpatient clinic every 3 months. During each follow-up visit, data from the 3-day voiding diary and symptom inventory using the O'Leary-Sant symptom score, as well as information from the voiding diary, pain VAS, and GRA were recorded. The largest voided volume in the 3-day voiding diary was considered as a measure of functional bladder capacity. At 6 months after the initial BoNT-A injection, patients were questioned about their bladder conditions. The urodynamic study and KCl test were performed at baseline and 6 months after BoNT-A treatment.

Statistical analysis

The results of the voiding diary, urodynamic study, ICSI, ICPI and pain VAS were compared between baseline and each treatment time point. Statistical comparisons between the groups were tested using a chi-square test for categorical variables, and a Wilcoxon rank-sum test for continuous variables. Statistical assessments were considered significant when P was < 0.05. Statistical analyses were performed using SPSS 15.0 statistical software (SPSS Inc, Chicago, IL).

Results

A total of 67 patients (60 women and 7 men, mean age 45.4 years old) were investigated in this study. All patients reported bladder pain at baseline, which was 5.3 2.2 on the VAS. The mean bladder pain score after the BoNT-A injection was 3.2 2.3. The difference was statistically significant ($P < 0.001$). By GRA criteria, 35/67(52.2%) patients had a GRA increase by 2 scales and reported significant improvement in bladder pain. Table 1 also summarizes the variables in symptom score, voiding diary, uroflowmetry, and MBC at baseline, 3 months, and 6 months. The ICSI and ICPI total score, functional bladder capacity, frequency, and nocturia all showed significant improvement after BoNT-A injection.

The adverse events were mostly manageable dysuria (24 patients, 35.8%); no episode of acute urinary retention developed. No patient needed clean intermittent catheterization, however, urinary tract infection developed in 4 patients (6%).

Discussion

In this prospective study with a significant number of patients, we found that intravesical injection of onabotulinumtoxin A was beneficial for relieving pain caused by refractory IC/PBS. Patients in this study were diagnosed with IC/PBS by strict application of NIDDK criteria by a single surgeon (HCK), minimizing diagnostic variability. All the cystoscopy-guided injections were performed by a single urologist, who was well acquainted with the procedure. There was a significant decrease in bladder pain scores at 3 and 6 months after intravesical BoNT-A injections. The incidences of serious adverse effects associated with this therapy were mild and reversible. In addition, our results demonstrated the BoNT-A has clinical effects to reduce bladder pain, increase functional bladder capacity, and quality of life, which are comparable to previous reports (11,12,19).

The definite etiology of IC/PBS remains unclear. The management of IC/PBS is directed to pain relief, as bladder pain is believed to drive bothersome lower urinary tract symptoms such as urgency and frequency. It is believed that IC/PBS may have multiple etiologies, including alterations in urothelial permeability, abnormal sensory nerve stimulation, and mast cell activation, which are simultaneously interrelated. This complexity of mechanisms results in the chronicity of IC/PBS and an unsatisfying response to single-modality treatment. Although a damaged urothelium has been speculated to cause chronic inflammation and subsequent hypersensitivity of the bladder, several intravesical therapies cannot eradicate bladder pain and bothersome urinary symptoms in most patients with IC/PBS (20,21), suggest-

Table 1. *The changes of end-point variables at baseline, 3 and 6 months after single BoNT-A injection in 67 patients with IC/PBS*

BoNT-A	Baseline	3M	6M	P value
ICSI	12.38±3.19	8.46±4.22	8.18±4.35	0.000
ICPI	11.2±2.98	6.87±4.17	7.00±4.42	0.000
OSS (ICSI+ICPI)	23.6±5.95	15.3±8.19	15.2±8.47	0.000
VAS	5.28±2.16	3.20±2.26	3.34±2.43	0.000
FBC	136±77.6	187±82.7	180±78.2	0.000
Frequency	14.5±6.34	10.8±4.81	10.0±4.10	0.000
Noturia	4.26±3.97	2.79±1.82	2.74±1.66	0.001
Qmax	13.3±4.68	13.2±5.31	17.1±19.5	0.150
Volume	247±108	237±121	234±130	0.570
PVR	13.9±34.5	38.8±64.5	44.5±75.7	0.002
CBC	261±108	278±144	282±158	0.288
GRA	0.33±0.77	1.38±1.00	1.41±0.99	0.000

BoNT-A: botulinum toxin type A, CBC: cystometric bladder capacity, FBC: functional bladder capacity, GRA: global response assessment, ICPI: interstitial cystitis problem indexes, ICSI: interstitial cystitis symptom indexes, OSS: O'Leary-Sant symptom score, PVR: postvoid residual, VAS: visual analog scale

ing restoration of epithelial integrity can only partially repair the damaged urothelial barrier but not the submucosal inflammation or possible central sensitization pain process that characterizes IC/PBS. Different irritative events of the pelvis or urinary bladder can produce neuropathic pain by peripheral and central sensitization.

Peripheral sensitization lowers the threshold for nociceptor discharge by inducing changes in the receptors themselves and/or by increasing the excitability of the pain terminal membrane (22). In IC/PBS, it is believed that IC also represents a visceral neuropathic pain syndrome mediated by upregulation of nerves in the pelvis, spinal cord, and brain. Previous studies have demonstrated that substance P and nerve growth factor released by mast cells are involved in the pathogenesis (23-25). These peptides are the neuropeptides thought to be most active in the process of neurogenic inflammation which might also reduce the threshold of the dorsal root ganglia and dorsal horn of the spinal cord. This induces central sensitization of pain transmission neurons which is essential to the development of chronic neuropathic pain (22).

BoNT-A acts by cleaving the SNAP-25 (Synaptosome-associated protein of 25 kd) complex in the presynaptic terminal, which prevents formation of the SNARE system. By this mechanism, the neurotransmitter vesicles cannot work at the presynaptic membrane, which decreases the release of neurotransmitters at thesynaptic cleft. Consequently, the release of accetycholine, CGRP, Substance-P and glutamate decreased and then the nociceptive fiber discharge reduced (26,27). Consistent with other studies, our results reproduce the positive effect BoNT-A on IC/PBS especially on the pain symptom

There are a significant number of clinical studies on the use of BoNT-A for IC/PBS, including 3 recent prospective nonrandomized studies. Pinto et al (19) demonstrated in an open exploratory study of 26 patients that trigonal injections of 100 U BoNT-A is effective for relieving pain and urinary daytime and nighttime frequency. They chose trigone as the injection site based on the concept that most nociceptive bladder afferents are concentrated in the trigone. Their results supported their hypothesis and the treatment remained effective in > 50% of the patients for 9 months. Smith et al (9) treated 13 patients with IC/PBS and reported a 69% success rate with a therapeutic duration of 9 months by submucosal injections in the trigone and floor of the bladder with 100 U or 200 U of BoNT-A (9). Their results also indicated that this procedure provided both symptomatic and functional improvements, which suggested that BoNT-A has an antinociceptive effect on bladder afferent pathways (9). Giannantoni et al (12) reported 85.7% of 15 patients who were treated by submucosal injections of the bladder trigone and lateral wall had

improvement, but the duration was only 3 months (12). In their long-term follow-up, the therapeutic effect decreased to 26.6% by 5 months and none had an effect by 12 months (12). The above-mentioned studies all suffered from a major drawback: the lack of a placebo group. Recently, the only randomized controlled study, as reported by Gottsch et al (28), failed to demonstrate the efficacy of BoNT-A injection for IC/PBS. However, their injection method was periurethrally and the dose was smaller, only 50 U (28).

We postulated that the relief of bladder pain by intravesical BoNT-A injection would include a reduction of neurogenic inflammation (29). Increased central c-Fos expression has been demonstrated in animal models of neurogenic detrusor overactivity and chronic bladder inflammation (30,31). BoNT-A has been demonstrated to reduce Fos-positive cells in the dorsal horn of formalin-challenged rat models (32). Multiple investigations have demonstrated that NGF has an important role in altered bladder sensory function and the development of referred hyperalgesia in response to bladder inflammation. Dmitrieva et al (32) identified that intravesical nerve growth factor (NGF) sensitized C-fiber and A bladder sensory afferents. Yoshimura et al (33) found that intrathecal NGF increased NGF expression in bladder afferents, induced bladder afferent hyperexcitability, and caused urinary bladder overactivity. These findings suggested that increased NGF levels in the afferent limb of the micturition reflex contributes to alterations in bladder sensory function (33). Increased bladder NGF expression via adenoviral delivery also induced voiding frequency as well as bladder overactivity (34). In addition, increased central-Fos expression after bladder distension and increased CGRP expression in the bladder and lumbosacral spinal cord were also identified after chronic bladder administration of NGF (35).

Taken together, an NGF-mediated reorganization of micturition reflex pathways are hypothesized to be involved in the pathomechanism of bladder overactivity and bladder pain. Reduction of NGF production could lead to inhibition of neurogenic inflammation and further peripheral desensitization (2). Concerning this point, this intensity of desensitization might be correlated with the efficacy of relieving bladder pain. BoNT-A has been demonstrated to have an anti-inflammatory effect on a cystitis rat model (36) and can reduce the bladder's NGF level after injection in IC/PBS patients resulting in satisfactory pain relief (37,38).

The major limitations of our present study included the lack of a control arm and that it was not randomized. Further well-designed randomized trials to confirm the efficacy of BoNT-A injection for pain relief in IC/PBS patients is needed.

Conclusion

This study is the largest study to date that supports BoNT-A intravesical injection and may be a potentially useful therapy to relieve pain and bothersome urinary symptoms for refractory IC/BPS.

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