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ORIGINAL ARTICLE

Intravesical injection of botulinum toxin A for treatment of interstitial cystitis/bladder pain syndrome: 10 years of experience at a single center in China

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Abstract
Introduction and hypothesis To evaluate the efficacy and safety of the intravesical injection of Chinese botulinum toxin A (BTX-A) in patients with interstitial cystitis/bladder pain syndrome (IC/BPS).
Methods Between January 2003 and June 2013, 124 women with IC/BPS were studied. Of these 124 patients, 66 were treated with BTX-A and 58 underwent bladder hydrodistention plus sodium hyaluronate (Cystistat) instillation. Intravesical injection of 100 U of Chinese BTX-A was immediately followed by cystoscopic hydrodistention under intravenous general anesthesia. The patients were evaluated using the O'Leary-Saint score, a visual analog scale pain score, a urinary frequency record and a quality of life questionnaire before treatment and 1 week, and 1, 3, 6 and 12 months after treatment.
Results Of the patients who received BTX-A injection, only 2 had acute urinary retention, 23 received a repeat injection, and 20 were lost to follow-up. Of the patients treated with hydrodistention plus Cystistat instillation, 2 had urinary tract infection, 11 switched to BTX-A injection at 6 months, and 23 were lost to follow-up. BTX-A was shown to remain effective for up to 6 months after treatment. After repeated Chinese BTX-A injections, symptoms improved significantly. Hydrodistention plus Cystistat remained effective for up to 3 months after treatment.
Conclusions Intravesical injection of Chinese BTX-A is a safe and effective therapeutic option for patients with IC/BPS. The average duration of the effect of one dose of Chinese BTX-A amongst the responders was 6 months. Repeated injection of Chinese BTX-A is safe and effective.

Keywords Interstitial cystitis · Bladder pain syndrome · Chinese botulinum toxin · Intravesical injection · Hydrodistention · Sodium hyaluronate

Author participation Y.G. collected the data, performed the statistical analysis, and drafted the manuscript. L.L. contributed to the conception and design of the study, analysis and interpretation of the data, and helped draft the manuscript. Both authors read and approved the final version of the manuscript.

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Introduction

The pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS) is not completely understood. The clinical features associated with IC/BPS include lower urinary tract symptoms (LUTS), such as bladder pain, frequency, and urgency. The current management of IC/BPS focuses on pain relief, as bladder pain is thought to trigger bothersome LUTS, such as urgency and frequency. Patients with IC/BPS typically have severe pain and an impaired quality of life (QOL). Existing treatments for IC/BPS generally fail to completely eradicate bladder pain and urinary frequency [1]. Botulinum toxin (BTX) is one of the most potent neurotoxins. It acts by inhibiting the release of neurotransmitters from nerve fibers and the urothelium [2–5].

The use of BTX type A (BTX-A, Botox; Allergan Pharmaceuticals Ireland) for the treatment of IC/BPS has been reported in a limited number of studies, and injected into the bladder wall appears to be a promising treatment for IC/BPS [6–9]; however, the efficacy and safety of Chinese BTX-A (Lantox; Lanzhou Institute of Biological Products in China, Lanzhou, China) for the treatment of IC/BPS has not been reported. We have previously reported data on the use of Chinese BTX-A in patients with neurogenic bladder, which

showed that BTX-A inhibits detrusor overactivity and reduces the incidence of lower urinary tract infections (UTIs) [10, 11]. We are frequently asked whether or not the effects and benefits of BTX-A injection can be attributed to hydrodistention, which is unavoidable during surgery under intravenous general anesthesia. No studies have answered this question.

In this retrospective study we included patients treated with hydrodistention plus sodium hyaluronate (Cystistat; H+C instillation) to ascertain the benefit or lack of benefit of hydrodistention. The purpose of the study was to evaluate the efficacy and safety of the intravesical injection of Chinese BTX-A for the treatment of IC/BPS, and to report 10 years of experience at a single center in China.

Materials and methods

Patient enrollment

This was a retrospective study. Patients with IC/BPS who had failed oral treatment with anticholinergics and tricyclic antidepressants were enrolled between January 2003 and June 2013. A diagnosis of IC/BPS was established based on characteristic symptoms and cystoscopic findings (glomerulation, petechiae, mucosal fissures, and ulcerations) [12], and the IC/BPS criteria of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [13]. All patients had been treated with at least two of the following medications for more than 1 year, but the symptoms remained unchanged or recurred: oral pentosan polysulfate, a tricyclic antidepressant, or an anticholinergic agent. All patients were informed that two forms of minimally invasive treatment were available: intravesical injections of Chinese BTX-A, and H+C instillation (Cystistat; Bioniche Teo, Canada). The patients were also informed of the possible complications associated with BTX-A injection, including generalized muscle weakness, difficulty urinating, transient urinary retention and UTIs, and complications associated with H+C instillation, including bleeding and UTIs. The patients were then permitted to choose one of the treatment methods. Thus, 66 patients were treated with intravesical injections of Chinese BTX-A, and 58 were treated with bladder H+C instillation.

All patients were hospitalized in the Department of Urology at the China Rehabilitation Research Center (CRRC) for treatment. The patients treated with BTX-A underwent cystoscopic hydrodistention and intravesical injection of 100 U of Chinese BTX-A under intravenous general anesthesia in the operating room. Each vial of BTX-A was diluted with 10 ml of normal saline, and 10 ml of solution containing 100 U of BTX-A was injected at 20 suburothelial sites. The injection needle was inserted into the detrusor and urothelium (trigone) using a 23-gauge cystoscopic injection needle (Cook Medical Incorporated, Bloomington, IN) via a rigid cystoscope (22F; Richard Wolf, Knittlingen, Germany). BTX-A (5 U in 0.5 ml of solution) was injected at each site. The 20 injection sites were as follows: trigone of the bladder (3 sites), posterior bladder wall (7 sites), and bilateral walls of the bladder (10 sites). Before and during BTX-A injection, the bladder was instilled with sufficient saline under an intravesical pressure of 80 cm of water for 5 min to achieve adequate visualization. After the BTX-A injections, a 14F urethral Foley catheter was inserted and was kept in place for 3 days.

The patients were discharged on the 7th day after treatment. Analgesics, tricyclic antidepressants, and/or antimuscarinics were discontinued after treatment. Oral antibiotics were prescribed before the injection and for 3 days after injection. H+C was instilled at an intravesical pressure of 80 cm of water for 5 min, after which Cystistat was instilled once a week during the first month, then once a month for 5 months. All of the above injections were completed by three trained senior urologists. This study was approved by the Ethics Committee at CRRC. Each patient was informed about the study rationale and procedures; written informed consent was obtained before treatment.

Clinical assessment

Patients were asked to maintain a 3-day voiding diary prior to treatment to record LUTS (frequency and urgency). The IC/BPS symptoms were assessed using the O'Leary-Saint score (OSS), which includes symptom and problem indices [14]. Pain was reported by self-assessment using a ten-point visual analog scale (VAS). Outcome measurements included a change in OSS, VAS score, urinary frequency, and QOL from baseline (before the initial BTX-A injection) to 12 months after the BTX-A injection, and the same scoring was applied for repeated H+C instillations over the time period. VAS pain score and urinary frequency were the two primary outcome measures; all other outcomes were secondary measures. The most important index for efficacy was VAS pain score. The treatment was considered effective when the VAS score and/or frequency improved by >50 % from baseline.

The patients were monitored in the outpatient clinic and by telephone 1 week, and 1, 3, 6 and 12 months after treatment. During each follow-up visit, data were recorded from the 3-day voiding diary and symptom inventory using the OSS, VAS score and QOL. The results were compared between baseline and each follow-up evaluation.

Data analysis

Continuous variables are presented as means ± standard deviation (SD), and categorical data are presented as number and percentage. Statistical comparisons between the groups were tested using repeated measures analysis of variance and *t* tests for variables. Statistical assessments with P values <0.05 were

considered significant. Statistical analyses were performed using SPSS 17.0 statistical software.

Results

The study included 124 women with IC/BPS. Of these patients, 66 were injected with Chinese BTX-A and 58 were treated with H+C. Of those receiving Chinese BTX-A, 2 patients had acute urinary retention (AUR) after the injection, 23 patients received at least one repeat injection cycle, and 20 patients were lost to follow-up. Of those receiving H+C, 2 patients had UTIs, 11 patients switched to BTX-A injections at 6 months, and 23 patients were lost to follow-up. Table 1 shows the symptom scores, including OSS, VAS scores, QOL and urinary frequency, in the two patient groups at baseline and during the follow-up period.

Baseline

The mean ages of the patients were 59 years in the BTX-A group and 57 years in the H+C group, and the treatment course was 48 and 49 months, respectively. The baseline scores for the two groups are shown in Table 1.

BTX-A group during follow-up

At 1 week after injection 5 patients showed no response in terms of VAS score and urinary frequency, and 2 patients had developed AUR. A significant response was seen in 59 of the 64 remaining BTX-A recipients. Thus, at 1 week the efficacy rate with a single dose was 92.2 % (59/64).

At 1 month 9 patients showed no response, and 1 patient received a repeat injection. A significant response was seen in 54 of the 63 remaining BTX-A recipients. Thus at 1 month the efficacy rate with a single dose was 85.7 % (54/63).

At 3 months 14 patients showed no response, 4 patients were lost to follow-up, and 3 patients received a repeat injection. A significant response was seen in 42 of the 56 remaining BTX-A recipients. Thus, at 3 months the efficacy rate with a single dose was 75 % (42/56).

At 6 months 28 patients showed no response, 5 patients were lost to follow-up, and 9 patients received a repeat injection. A significant response was seen in 14 of the 42 remaining BTX-A recipients. Thus, at 6 months the efficacy rate with a single dose was 33.3 % (14/42).

At 12 months 11 patients were lost to follow-up, and 10 patients received a repeat injection. None of the 21 remaining BTX-A recipients continued to benefit. Thus, at 12 months the efficacy rate with a single dose was 0 % (0/21).

H+C group during follow-up

At 1 week 5 patients showed no response. A significant response was seen in 53 of the H+C recipients. Thus, at 1 week the efficacy rate was 91.4 % (53/58).

At 1 month 15 patients showed no response. A significant response was seen in 41 of the H+C recipients. Thus, at 1 month the efficacy rate was 73.2 % (41/56).

At 3 months 27 patients showed no response. Nine patients were lost to follow-up. The OSS, VAS score and QOL were significantly improved at 3 months; there was no significant improvement in urinary frequency (P=0.096). A significant response was noted in 20 H+C recipients. Thus, at 3 months the efficacy rate was 42.6 % (20/47).

At 6 months only 1 patient was still benefitting from H+C treatment, 11 patients chose BTX-A injections to alleviate the symptoms, and 14 patients were lost to follow-up. None of the scores had improved significantly at 6 months. Thus, at 6 months the efficacy rate was 4.5 % (1/22).

At 12 months, of the two patients compliant with the scheduled follow-up, pain and urinary frequency recurred. The

Table 1 Symptom scores at baseline, and at 1 week, and 1, 3, 6 and 12 months after treatment in patients in the BTX-A injection group and the H+C group (values are means ± SD)

	Baseline	1 week	1 month	3 months	6 months	12 months
BTX-A						
OSS	34.3±1.7	19.3±6.2*	25.0±4.3*	31.2±2.4*	33.4±1.5*	34.4±1.5
VAS	9.4±0.9	2.3±1.8*	4.2±1.7*	8.1±1.3*	8.9±1.0*	9.3±0.7
Frequency	47.9±11.2	32.4±8.7*	34.9±9.2*	42.6±10.9*	45.4±10.9*	47.7±11.9
QOL	5.3±0.6	3.1±0.8*	3.6±0.9*	4.8±0.5*	5.1±0.5	5.3±0.6
H+C						
OSS	34.7±1.5	19.4±6.1*	31.4±2.5*	34.2±1.5*	35.1±1.0	35.5±0.7
VAS	9.2±0.8	4.0±1.6*	8.1±1.2*	7.9±1.3*	9.6±0.8	9.5±0.7
Frequency	48.5±11.2	35.3±9.5*	43.5±10.6*	48.2±11.7	49.2±12.4	49.5±3.5
QOL	5.4±0.6	3.6±0.9*	4.8±0.6*	5.3±0.6*	5.5±0.6	5.5±0.7

*P < 0.05, vs. the corresponding baseline value

other patients switched to other treatments and were lost to follow-up. The efficacy rate was 0 %.

Table 1 shows that the effects of BTX-A and H+C treatment persisted for 6 and 3 months, respectively. Figure 1 shows the improvements in VAS and urinary frequency compared to the baseline scores in responders who received a single dose of Chinese BTX-A or H+C. The average duration of effect of one dose of Chinese BTX-A amongst the responders was 6 months.

BTX-A repeat injections

In this study, 23 patients received repeat Chinese BTX-A injections. The patients were divided into the following three groups: group 1, two or more injection cycles; group 2, three or more injection cycles; and group 3, four injection cycles. The time between cycles, and the OSS, VAS score, urinary frequency, and QOL at 1 week, and 1, 6 and 12 months after treatment are shown in Table 2. The VAS score and urinary frequency had improved significantly at 1 week, and 1, 3 and 6 months after each BTX-A injection compared to the baseline values.

Table 2 Clinical scores in patients who received repeat injections of Chinese BTX-A (values are means ± SD)

	Group 1	Group 2	Group 3
No. of patients	23	5	1
Time between injection cycles (months)	4.8±2.1	5.0±2.4	5
Efficacy rate 1 week after injection (%)	91.3	80	100
VAS			
1 week	3.1±1.8*	3.3±1.6*	4
1 month	3.9±1.8*	3.8±1.9*	4
6 months	8.8±1.4*	8.5±1.3*	8
12 months	9.5±1.2	9.4±1.1	9
Frequency			
1 week	28.9±7.7*	31.0±8.0*	23.0±2.0*
1 month	32.9±11.0*	33.7±11.1*	31.0±5.1*
6 months	43.7±9.9*	44.9±7.7*	39.0±4.1*
12 months	47.9±11.5	47.8±11.9	48.0±5.7
QOL			
1 week	3.0±0.8*	3.0±0.8*	3*
1 month	3.0±0.8*	3.5±0.8*	3*
6 months	4.9±0.7*	5.0±0.8*	5
12 months	5.5±0.8	5.5±0.7	6

*P <0.05, vs. corresponding baseline scores

Discussion

In our clinical practice involving the treatment of IC/BPS, intravesical injection of BTX-A with bladder filling is inevitably accompanied by hydrodistention, and the hydrodistention is always followed by Cystistat bladder instillation as combination therapy. The results of the current study demonstrated that Chinese BTX-A injection and H+C instillation are effective treatments for IC/BPS at 1 week, and 1 and 3 months in patients refractory to oral treatment. H+C instillation was ineffective at 6 months after treatment (Table 1). Urinary frequency in patients who underwent H+C instillation had returned to the baseline level 3 months after treatment. H+C was most effective 1 week after treatment and the effect persisted for 3 months. These findings suggest that BTX-A injection, including hydrodistention, had a superior duration of effect and higher response rate, and may be superior to H+C instillation, although not significantly; thus, the benefits of BTX-A were confirmed.

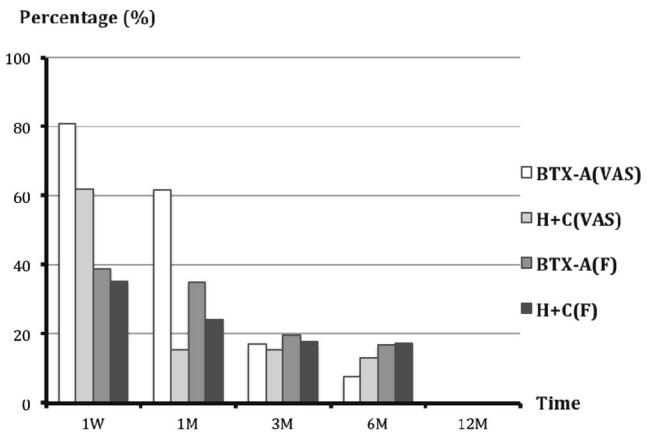

Fig. 1 VAS scores and urinary frequency (*F*) at 1 week, and 1, 3, 6 and 12 months after treatment in relation to the baseline scores in responders who received a single dose of BTX-A or H+C

Intravesical injection of Chinese BTX-A is an effective treatment modality for patients with IC/BPS at 1 week, and at 1, 3 and 6 months after treatment, but injection of Chinese BTX-A had lost its efficacy by 12 months after treatment. Chinese BTX-A was most effective in patients with IC/BPS 1 week after treatment, followed by 1 and 6 months (when the scores approached the baseline state). Chinese BTX-A was without effect 12 months after treatment (Table 1). Chinese BTX-A is most effective for 1 week, and the effect persisted for approximately 6 months. Specifically, the efficacy rates for Chinese BTX-A in patients with IC/BPS were 92.2 % at 1 week, 85.7 % at 1 month, 75 % at 3 months, 33.3 % at 6 months, and 0 % at 12 months. Similarly, the efficacy rates for H+C instillation in patients with IC/BPS were 91.4 % at 1 week, 73.2 % at 1 month, 42.6 % at 3 months, 4.5 % at 6 months, and 0 % at 12 months. Thus, at 6 months after treatment, 22 % of patients who received a single injection of BTX-A continued to show a response in contrast to only 3 % of those who received H+C instillation, suggesting a clear benefit of BTX-A.

Chinese BTX-A was therefore shown to be an effective therapeutic modality in patients with IC/BPS and the effect was superior to that of H+C instillation. In addition, our results demonstrated that Chinese BTX-A reduces bladder pain and urinary frequency, and increases QOL, findings that are in agreement with those of a previous study [15]. No UTIs were reported in the BTX-A group, which may reflect the effectiveness of prolonged use of antibiotics; two infections occurred in the Cystistat group, in which antibiotics were not used with repeat catheterizations. The reason for leaving the catheter in place for 3 days was to prevent untoward effects (e.g., pain, hematuria, and incomplete bladder emptying due to surgery) and because the patients were hospitalized for 7 days. The reason for the high number of patients lost to follow-up was that all patients came from different areas of China, a vast territory, and it was difficult to maintain contact with some patients. We considered the influence of the high drop-out rate, low follow-up rate, and switch to the other treatment, all of which are avoidable, on outcomes.

We also evaluated the efficacy and safety of Chinese BTX-A after repeat injections. Previous studies [16, 17] have shown that repeat BTX-A injections are effective and safe in patients with IC/BPS, and provide better long-term success rate than a single injection. The efficacy of Chinese BTX-A persisted for approximately 6 months after repeat injections. The time between the first and second injection cycles was 4.8± 2.1 months, the time between the second and third injection cycles was 5.0±2.4 months, and the time between the third and fourth injection cycles was 5 months. Of note, some patients who achieved relief after the first injection did not achieve relief after the second injection. We did not find a direct relationship between treatment efficacy and the number of injection cycles, which may be related to the injection method. Indeed, a limitation in this study was that we were unable to observe the patients continually and therefore could not regularly assess the effects of repeated injections on a large scale.

The etiology of IC/BPS remains unclear. It is believed that it may have multiple etiologies, including alterations in urothelial permeability, abnormal sensory nerve stimulation, and mast cell activation, which are interrelated. The complexity of this mechanism results in the chronicity of IC/BPS and the unsatisfactory response to conventional treatment. It has been speculated that a damaged urothelium causes chronic inflammation and subsequent hypersensitivity of the bladder, and thus intravesical therapies cannot eradicate bladder pain and bothersome urinary symptoms in most patients with IC/BPS [18, 19]. 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/BPS. BTX-A acts by cleaving the 25-kDa synaptosome-associated protein (SNAP-25) complex in the presynaptic terminal, which prevents formation of the SNARE system. Thus, the neurotransmitter vesicles cannot function at the presynaptic membrane, which decreases the release of neurotransmitters at the synaptic cleft. Consequently, the release of acetylcholine, CGRP, substance-P and glutamate is decreased and the nociceptive fiber discharge is reduced [20, 21]. Consistent with the findings of other studies, our results confirm the efficacy and safety of intravesical injection of Chinese BTX-A to treat patients with IC/BPS refractory to oral treatment.

Some points are worth emphasizing. The dose of Chinese BTX-A for treating IC/BPS is 100 U. It is possible that a higher dose could result in a better effect, so further study on optimal dosing is needed. Because the effect of Chinese BTX-A is transient, repeat injections have been reported to be effective. BTX-A injection into the trigone could more effectively relieve IC/BPS symptoms. We did not identify a difference between Chinese BTX-A and onabotulinumtoxin A in a review of the literature. New methods and better combination drug therapy will likely be developed. The most important limitation of the current study was the nonprospective and nonrandomized design, but there was a lengthy follow-up and the empirical nature of the research reflected real-life outcomes.

Conclusions

The results of this study show that intravesical injection of Chinese BTX-A reduces bladder pain and LUTS, and is therefore suitable for the treatment of patients with IC/BPS refractory to oral treatment, and the effect of treatment persists for approximately 6 months. Repeat injections of Chinese BTX-A were also shown to be effective and safe.

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Conflicts of interest None.

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