Prospective Evaluation

Intravesical Botulinum Toxin A Injections Do Not Benefit Patients with Ulcer Type Interstitial Cystitis

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Background: Ulcer type and non-ulcer type interstitial cystitis/bladder pain syndromes (IC/BPS) are considered different disease entities. Thus, intravesical botulinum toxin A (BoNT-A) treatment outcomes could differ for each entity.

Objectives: To evaluate and compare the treatment outcomes of BoNT-A injections for treatment of each IC/BPS type.

Study Design: Prospective interventional study.

Setting: Tertiary medical center affiliated with Buddhist Tzu Chi General Hospital and Tzu Chi University, Taiwan.

Methods: Forty-four consecutive patients with IC/BPS for whom conventional treatments failed were prospectively enrolled in this study. Patients were classified as having ulcer (n = 10) or non-ulcer (n = 30) IC/BPS based on their previous cystoscopic findings.

Intervention: All patients received 4 sets of intravesical BoNT-A injections (100 U in 40 suburothelial injections) every 6 months. The primary end-point was the global response assessment (GRA) 6 months after the fourth set of BoNT-A injections. Secondary end-points included the O'Leary-Sant score (OSS) including symptom indexes (ICSI) and problem indexes (ICPI), visual analog scale (VAS) pain score, voiding diary, and urodynamics variables.

Results: After 4 sets of BoNT-A injections, 15 patients with non-ulcer IC/BPS had GRA scores ≥ 2, while the other 15 had GRA scores < 2. All 10 patients with ulcer IC/BPS had GRA scores < 2 at the study end-point (treatment failure). At baseline, patients with ulcer IC/BPS had significantly higher daytime frequency, nocturia, smaller functional bladder capacity, smaller voided volume, greater VAS, smaller maximal bladder capacity, and greater glomerulation grade than did patients with non-ulcer IC/BPS. After 4 sets of BoNT-A injections, patients with non-ulcer IC/BPS and GRA scores ≥ 2 or < 2 all had significantly decreased ICSI, ICPI, OSS, VAS pain scores, frequency episodes, and increased functional bladder capacity. However, patients with ulcer IC/BPS showed no significant change in any clinical or urodynamic variable. After failure of repeated BoNT-A injections, all 10 patients with ulcer IC/BPS underwent transurethral electrocauterization of their ulcers, which resulted in immediate pain relief.

Limitations: Lack of a control arm in this study.

Conclusion: Repeated intravesical BoNT-A injections provided effective treatment outcomes at the end-point in half of the patients with non-ulcer IC/BPS, but did not benefit any patient with ulcer type IC/BPS. Ulcer type IC/BPS should be treated as a different disease than non-ulcer IC/BPS.

Institutional Review: This study was approved by the Institutional Review Board of the Tzu-chi General Hospital (TCGH 100-06).

Key words: Botulinum toxin, interstitial cystitis, bladder pain syndrome, intravesical treatment, Hunner's ulcer

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is characterized by bladder pain associated with urgency, frequency, nocturia, and sterile urine. The diagnosis of IC/BPS is based on symptoms and urological findings, including characteristic cystoscopic features after hydrodistention under anesthesia (1). IC/BPS is usually classified into classic (ulcer) and non-ulcer types based on cystoscopic findings (2). Classic IC, also called Hunner's ulcer, is characterized by observable bladder ulcerations after hydrodistention (3). Non-ulcer IC, also called early IC, is characterized by glomerulations and petechia formation after hydrodistention under anesthesia. Although many pathogeneses of IC/BPS are proposed, the actual etiology remains unclear (4).

Hunner's ulcer is found in about 10% – 20% of patients with IC/BPS (5). Some investigators asserted that patients with Hunner's ulcer have a tendency to be older and have smaller bladder capacity and more urinary frequency than patients without the ulcer (6,7). Nonetheless, the clinical symptoms and characteristics do not significantly differ between ulcer and non-ulcer IC/BPS. Cystoscopy is needed to identify patients with Hunner's ulcers accurately (8). In clinical experience, patients with IC/BPS and bladder ulceration often suffer from intractable lower abdominal pain, and the pain usually does not respond to medical treatment. A recent study on urinary chemokines in ulcer type IC/BPS revealed a significant 5- to 20-fold increase in chemokines CXCL-10 and 1, interleukin-6, and nerve growth factor, suggesting ulcer and non-ulcer IC/BPS are different disease entities with different paracrine signaling (9).

The pathophysiology of IC/BPS is not fully understood. Current treatments are usually unsuccessful in completely eradicating bladder pain and increasing functional bladder capacity (FBC) (10). Denudation or thinning of the bladder urothelium is found in bladder mucosal biopsies, suggesting altered urothelial homeostasis and increased urothelial apoptosis could be responsible for the loss of epithelial integrity (11). The suburothelial space immediately below the basal lamina is well supplied with sensory nerves, which transmit the sensation of bladder fullness and the response to bladder inflammation (12,13).

Botulinum toxin type A (BoNT-A) is one of the most powerful neurotoxins capable of inhibiting the release of neurotransmitters from the nerve fibers and urothelium (14-17). In chemically induced cystitis in rats, injection of BoNT-A into the detrusor muscle increased bladder capacity and compliance (18). In patients with IC/BPS, inhibition of neuroplasticity of sensory fibers in the suburothelial space by intravesical BoNT-A injections targets pain and sensory urgency (19).

BoNT-A is reported as effective for the treatment of neurogenic and idiopathic detrusor overactivity (20,21); however, the application of BoNT-A to IC/BPS is reported in only a few studies (22-24). BoNT-A reduced bladder pain, modulated bladder sensation, and reduced chronic inflammation in the central nervous system in several animal and human experiments (16,19,23,25). Although BoNT-A injections seemed promising for treating symptoms of IC/BPS, long-term follow-up did not show successful outcomes after a single injection (26). A previous study showed that at the 5-month follow-up the beneficial effects persisted in 26.6% of cases, and an increased visual analog scale (VAS) score were observed compared to baseline. At 12 months after treatment pain recurred in all patients (26). The limited long-term success is possibly due to the poorly sustained therapeutic effect of a single BoNT-A injection on chronic bladder inflammation. Our previous study has demonstrated that repeated BoNT-A injections provide a better treatment outcome and longer therapeutic duration (27).

Although BoNT-A showed potential as an IC/BPS treatment, we found a lack of studies comparing the effects of BoNT-A between ulcer and non-ulcer IC/BPS. The purpose of this study was to evaluate the differences in efficacy of repeated intravesical BoNT-A injections between these 2 types of IC/BPS.

Methods

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 before enrolling in the study; written, informed consent was obtained before treatment.

Forty-four consecutive patients with IC/BPS who had experienced conventional treatment failure were prospectively enrolled in this study from January 2008 to January 2012. A diagnosis of IC/BPS was established based on characteristic symptoms and cystoscopic findings (28). All patients had been treated with at least 2 of the following medications: oral pentosanpolysulphate or a tricyclic antidepressant and intravesical instillations of heparin or hyaluronic acid for more than one year, but their symptoms remained unchanged. Patients were classified as having ulcer (n = 10) or non-ulcer (n = 30) IC/BPS based on their cystoscopic findings.

Patients kept a 3-day voiding diary prior to treatment to record FBC and episodes of urinary frequency

and nocturia. The IC/BPS symptoms were assessed using the O'Leary-Sant Symptom Score (OSS) including symptom indexes (ICSI) and problem indexes (ICPI) (29). The ICSI and ICPI contain 4 items that measure the patient's symptom severity and perception on the urgency and frequency of urination, nighttime urination, and pain or burning in the bladder. The ICSI and ICPI index scores are the sum of the item scores (range: 0 - 20 for ICSI and 0 - 16 for ICPI). The pain score was reported by self-assessment using a 10-point VAS system. Additionally, patients were informed of the possible complications associated with BoNT-A injections such as generalized muscle weakness, difficult urination, transient urinary retention, and urinary tract infections.

Video-urodynamic studies were performed at baseline and end-point by standard procedures using a 6-Fr dual channel catheter and an 8-Fr rectal balloon catheter. Cystometric studies were performed with warmed normal saline at a filling rate of 20 mL/min. All descriptions and terminology in this report are in accordance with the recommendations of the International Continence Society (30).

After the video-urodynamic studies, a maximum of 40 mL of 0.4 M potassium chloride solution was infused slowly into the bladder and the test was regarded as positive when painful (increased VAS pain score ≥ 2) or urgency sensation was elicited compared to normal saline infusion during the prior urodynamic study (31). The urodynamic parameters included first sensation of bladder filling, first desire to void, urge sensation to void, cystometric bladder capacity, detrusor pressure, maximum flow rate during voiding, and post-void residual volume.

All patients were scheduled to receive 4 sets of intravesical BoNT-A injections, one set every 6 months for 2 years regardless of whether or not symptoms improved. In this study design, patients were recommended to receive 4 injections; however, if patients had satisfactory symptom relief and did not desire to go further, the treatment will stop at the second or third injection. The primary end-point was the global response assessment (GRA) at 6 months after the fourth set of BoNT-A injections. The treatment outcomes were assessed using the GRA (32). Patients rated their bladder symptoms compared with baseline on a 7-point centered scale from -3 to +3. Patients with GRA scores ≥ 2 after treatment were considered to have successful treatment outcomes. Otherwise, the treatment was considered to have failed.

Patients were admitted to the hospital for the treatment. They received intravesical injections of 100 U of BoNT-A (onabotulinumtoxin-A, Allergan, Irvine, CA, USA) in each session. Each vial of BoNT-A was diluted with 20 mL of normal saline and 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 cystoscopic injection instrument (22 Fr, Richard Wolf, Knittlingen, Germany). After BoNT-A injection, cystoscopic hydrodistention was performed under intravenous general anesthesia in the operating room to an intravesical pressure of 80 cm of water for 15 minutes and the maximal bladder capacity under hydrodistention was recorded. When glomerulations, petechia, and mucosal fissure developed after bladder deflation, they were graded from 0 to 4, indicating none, mild, moderate, severe, and ulceration, respectively (28).

After the BoNT-A injections and hydrodistention, a 14-Fr urethral Foley catheter was inserted and remained for one day; patients were discharged on the next day. Oral antibiotics were prescribed for 7 days. Patients were monitored in the outpatient clinic 2 weeks later. Analgesic and tricyclic antidepressant medications were routinely discontinued immediately after treatment; however, morphine was allowed as a rescue medication for pain control after the injection procedure. The patients were monitored in the outpatient clinic monthly for 6 months. During each follow-up visit, data from the 3-day voiding diary and symptom inventory using the OSS, ICSI, ICPI, pain VAS, and GRA were recorded. The largest voided volume in the 3-day voiding diary was considered the measure of FBC. BoNT-A injection and hydrodistention were repeated 6 months after the first treatment and patients were monitored in the same way. The results of the 3-day voiding diaries, urodynamic studies, OSS, ICSI, ICPI, and pain VAS were compared between baseline and end-point (6 months after the last injection). All variables were also compared between ulcer and non-ulcer IC/BPS. Because half of the data did not follow a normal distribution, continuous variables are presented as median (interquartile range), and categorical data are presented as numbers and percentages (%). Statistical comparisons between the groups were tested using the chi-square test for categorical variables, and the Wilcoxon rank sum test for continuous variables. Statistical assessments were considered significant when $P < 0.05$. Statistical analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, IL).

Results

There were 10 patients with ulcer and 30 patients with non-ulcer IC/BPS enrolled in this study and all the patients were women. After 4 sets of BoNT-A injections, 15 (50%) of the patients with non-ulcer IC/BPS had GRA scores ≥ 2, while the other 15 (50%) had GRA scores < 2. All 10 patients with ulcer type IC/BPS had GRA scores < 2 at the study end-point. The median patient age was significantly older in patients with ulcer (57.5 [53, 66] years) than non-ulcer IC/BPS with GRA scores ≥ 2 (45 [38, 56]) or GRA scores < 2 (45 [40, 56]) (all $P < 0.01$).

At baseline, ICSI was similar between patients with ulcer and non-ulcer IC/BPS. There was no significant difference in the baseline symptom scores or cystoscopic findings between patients with non-ulcer IC/BPS with GRA scores ≥ 2 and GRA scores < 2. However, patients with ulcer IC/BPS had significantly greater daytime frequency, nocturia, smaller FBC, smaller voided volume, greater VAS pain score, smaller maximal bladder capacity, and a higher grade of glomerulations than did patients with non-ulcer IC/BPS (Table 1). The urodynamic studies at baseline showed significantly smaller cystometric bladder capacity and voided volume in patients with ulcer than non-ulcer IC/BPS (Table 2). All patients had positive potassium chloride (KCl) tests, but patients with ulcer IC/BPS had more intense bladder pain elicited immediately after instillation of KCl solution than those with non-ulcer IC/BPS.

After all 4 sets of BoNT-A injections, patients with non-ulcer IC/BPS and GRA scores ≥ 2 had significantly decreased ICSI, ICPI, OSS, pain VAS, frequency and nocturia episodes, and increased FBC, cystometric bladder capacity, first sensation of bladder filling, first desire to void, post-void residual volume, and decreased detrusor pressure. Patients with non-ulcer IC/BPS and GRA scores < 2 also had decreased ICSI, ICPI, OSS, VAS, frequency

Table 1. *The changes of voiding diary and cystoscopic findings after repeated BoNT-A injections among ulcer and non-ulcer IC/BPS subgroups.*

	Ulcer (N = 10)	**Non-ulcer (GRA ≥ 2) (N = 15)**	**Non-ulcer (GRA < 2) (N = 15)**	***P* value**
Frequency (times/d)				
BL	20 (14, 27.5)	15 (10, 15)	15 (8, 17)	A v B P = 0.173
Post-Tx	20 (10, 28.8)	8 (6, 8)	8 (7, 10)	A v C P = 0.721
Change	2 (0, 8.8)	6 (4, 9) *	5 (0, 7) *	B v C P = 0.252
Nocturia (times/d)				
BL	6 (4, 13.8)	3 (1, 5)	3 (2, 5)	A v B P = 0.357
Post-Tx	9 (3.5, 13.8)	2 (1, 3)	2 (2, 3)	A v C P = 0.429
Change	0.5 (-3.8, 1.8)	1 (0, 3)*	1 (0, 2)	B v C P = 0.597
FBC (mL)				
BL	80 (30, 100)	150 (100, 220)	100 (100, 200)	A v B P = 0.020
Post-Tx	60 (32.5, 138)	300 (200, 350)	200 (170, 300)	A v C P = 0.031
Change	0 (-35, 22.5)	-150(-200,-100)*	-100 (-150, 0) *	B v C P = 0.225
MBC (mL)				
BL	450 (300, 688)	700 (550, 950)	650 (600, 900)	A v B P = 0.673
Post-Tx	525 (388, 800)	750 (600, 900)	800 (700, 1000)	A v C P = 0.164
Change	25 (-150, 375)	-50 (-150, 0)	-100 (-200, 50)*	B v C P = 0.381
Glomerulation (grade)				
BL	3 (2, 4)	2 (1, 2)	1 (1, 2)	A v B P = 0.307
Post-Tx	3 (1. 5,4)	1 (0, 1)	1 (1, 2)	A v C P = 0.543
Change	0 (-1.5, 1.5)	1 (0, 1) *	0 (0, 1)	B v C P = 0.319
GRA (score)				
BL	0 (-1, 0.75)	0 (0, 1)	1 (0, 1)	A v B P = 0.001
Post-Tx	0 (-0.75, 1.8)	3 (2, 3)	2 (1, 2)	A v C P = 0.056
Change	0 (-1, 0.75)	-2 (-3, -2) *	-1 (-1, -1) *	B v C P = 0.000

Data are expressed as median (interquartile range), *P* values indicate difference of change from baseline to endpoint among groups.
BoNT-A: botulinum toxin A; FBC: functional bladder capacity; GRA: global response assessment; MBC: maximal bladder capacity; Post-Tx: post treatment

Table 2. *The changes of urodynamic variables after repeated BoNT-A injections among ulcer and non-ulcer IC/BPS subgroups.*

	(A) Ulcer (N = 10)	No Ulcer (GRA ≥ 2) (N = 15)	No Ulcer (GRA < 2) (N = 15)	*P* value
FSF (mL)				
BL	88.5 (51, 129)	130 (88, 157)	109 (86, 156)	A v B P = 0.179
Post-Tx	136 (36, 155)	167 (130.8, 225)	164 (124, 191)	A v C P = 0.132
Change	0 (-45, 15)	-47 (-125, -3) *	-68 (-99.5, -2.5)	B v C P = 0.961
FD (mL)				
BL	126 (90, 185)	163 (140, 210)	181 (131, 249)	A v B P = 0.056
Post-Tx	151 (51, 195)	248 (205, 298)	234 (187.5, 302)	A v C P = 0.190
Change	-20 (-60.3, 13.5)	-89 (-175, -31) *	-64 (-126, -14.8) *	B v C P = 0.622
US (mL)				
BL	110 (76.5, 147)	232 (201, 277)	218 (164, 307)	A v B P = 0.739
Post-Tx	173 (110, 180)	267 (216, 328)	225 (140, 356)	A v C P = 0.245
Change	-35 (-18, -23.5)	-33 (-77.3, -8.3)	-5 (-26.5, 47.5)	B v C P = 0.144
CBC (mL)				
BL	142 (80, 175)	316 (249, 391)	305 (201, 271)	A v B P = 0.205
Post-Tx	110 (99, 269)	379 (328, 483)	395 (248,489)	A v C P = 0.447
Change	-13 (-127, 48)	-69 (-237, 6.5) *	-64 (-175, 36)	B v C P = 0.681
Pdet (cmH_2O)				
BL	18 (11, 27.8)	20 (19, 31)	22 (16, 29)	A v B P = 0.061
Post-Tx	22 (10, 29)	16.5 (6.3, 25.5)	27 (15, 30)	A v C P = 0.964
Change	0 (-8, 7)	10 (5, 14) *	0 (-7, 11)	B v C P = 0.089
Qmax (mL/s)				
BL	12 (8, 15)	15.5 (13, 18)	12 (9.8, 17.5)	A v B P = 0.653
Post-Tx	12.3 (8, 14)	15.5 (6.8, 22)	13 (9.5, 15.8)	A v C P = 0.932
Change	-0.2 (-2, 1)	-1 (-6, 4.5)	1 (-3, 4)	B v C P = 0.717
Volume (mL)				
BL	142 (80, 175)	312 (249, 372)	260 (176, 356)	A v B P = 0.941
Post-Tx	104 (89, 169)	306 (251, 432)	337 (215, 399)	A v C P = 0.353
Change	-9 (-27, 58)	-12.5 (-228, 81.8)	-51 (-165, 38.5)	B v C P = 0.643
PVR (mL)				
BL	0 (0, 3)	10 (0, 10)	8 (0, 62.5)	A v B P = 0.879
Post-Tx	10 (4, 70)	35 (0, 85)	10 (0, 105)	A v C P = 0.940
Change	-10 (-70, 0) *	-30 (-77.5, 0) *	-10 (-85, 0)	B v C P = 0.640

Data are expressed as median (interquartile range), *P* values indicate difference of change from baseline to endpoint among groups.
BL: baseline, BoNT-A: botulinum toxin A, CBC: cystometric bladder capacity, FSF: first sensation of filling, FD: first desire to void, GRA: global response assessment, Pdet: detrusor pressure, Post-Tx: post treatment, PVR: postvoid residual, Qmax: maximum flow rate, US: urge sensation to void

episodes, and increased FBC, and increased maximal bladder capacity. Patients with non-ulcer IC/BPS and GRA scores ≥ 2 had significantly greater improvement than those with non-ulcer IC/BPS and GRA scores < 2 for ICSI ($P = 0.007$), ICPI ($P = 0.016$), and OSS ($P = 0.004$). However, patients with ulcer IC/BPS showed no significant change in any clinical or urodynamic variable. The improvement of IC/BPS symptoms and pain VAS were significantly less than for non-ulcer IC/BPS (Fig. 1).

After failure of repeated BoNT-A injections, all 10 patients with ulcer IC/BPS underwent transurethral electrofulgaration of their ulcers. Seven of them had immediate pain relief within 3 days after electrofulgaration. However, bladder pain recurred in 5 patients and a second electrofuguraton was performed to ablate the residual bladder ulcers. The pain symptoms were relieved after this second procedure.

The pathology reports of the bladder biopsies for ulcer IC/BPS revealed lymphocyte infiltration with chronic ulceration and granulation tissue and one biopsy showed eosinophilic cystitis. Mast cells and macrophages were identified in the bladder mucosa by immunohistochemical staining with c-kit and CD 68, respectively.

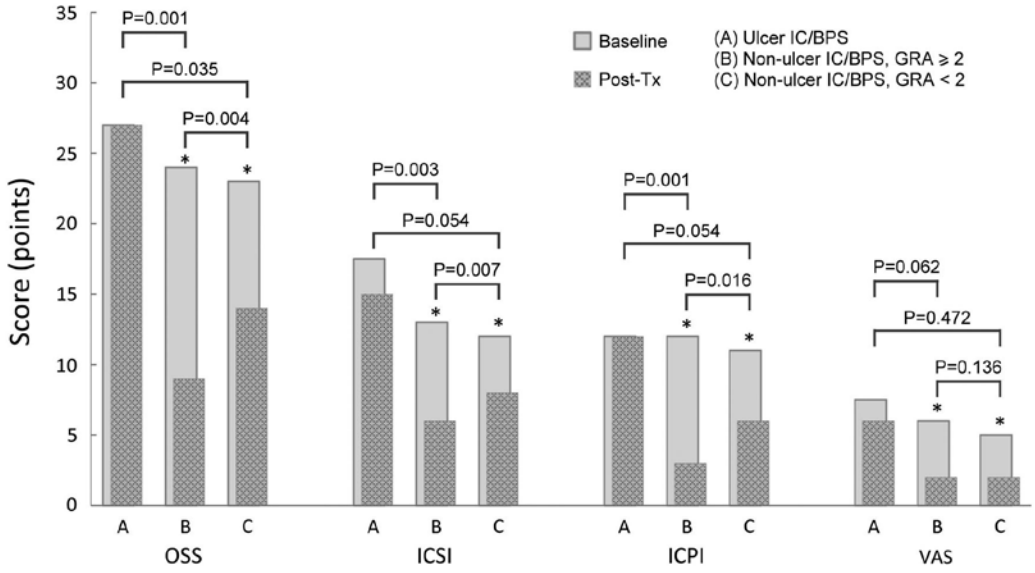

Fig. 1. *Changes of the median values of O'Leary-Sant Score (OSS), interstitial cystitis symptom index (ICSI), interstitial cystitis problem index (ICPI), and pain visual analog score (VAS) among (A) 10 patients with ulcer IC/BPS, (B) 15 patients with non-ulcer IC/BPS with GRA ≥ 2, and (C) 15 patients with non-ulcer IC/BPS with GRA < 2 at baseline and after BoNT-A injections. Asterisks indicate significant differences of changes of variables from baseline to end-point within group. P values indicate difference between IC/BPS subgroups.*

Discussion

The results of this study demonstrated that repeated intravesical BoNT-A injections improved IC/BPS symptoms, increased FBC and cystometric bladder capacity, and relieved pain in 50% of patients with non-ulcer IC/BPS, but did not benefit patients with ulcer IC/BPS.

A review of previous investigations of BoNT-A treatment of IC/BPS showed variable results. Smith et al (22) reported a 67% success rate for BoNT-A injections, with a therapeutic duration of 9 months. Giannantoni et al (23) reported 85.7% of patients had initial improvement, but the duration was only 3 months. Our recent study revealed that single intravesical injection of BoNT-A followed by hydrodistention produced significantly better clinical results than hydrodistention alone (33). In a recent clinical trial, a satisfactory success rate with a longer therapeutic duration occurred in patients receiving 4 repeated BoNT-A injection sessions, suggesting repeated BoNT-A injections are mandatory for better success (27). The evidence of this study suggests that patients with ulcer IC/BPS are poor candidates for BoNT-A treatment.

BoNT-A has an anti-inflammatory effect on cystitis in rats (22). It reduces bladder nerve growth factor levels after injection in non-ulcer IC/BPS patients, yielding satisfactory pain relief (34). A significant, transient reduction in urinary nerve growth factor and brain-derived nerve growth factor was also observed in IC/BPS patients after trigonal BoNT-A injections (35). We confirmed that pain relief in IC/BPS patients after repeated BoNT-A injections was significantly more prominent in patients with non-ulcer IC/BPS than ulcer IC/BPS. The improvement in bladder capacity and frequency of nocturia episodes after treatment were also found only in patients with non-ulcer IC/BPS. These results suggest that bladder pain and bladder hypersensitivity in ulcer and non-ulcer IC/BPS occur through different pathways, which could explain, at least in part, why the anti-inflammatory response of intravesical BoNT-A injection is ineffective in ulcer IC/BPS.

Although 15 patients with non-ulcer IC/BPS did not have significant improvement after BoNT-A injections as measured by GRA, the changes of frequency, MBC, and symptom score were still significant. We hypoth-

esize these patients might have a suboptimal therapeutic effect from BoNT-A injections. A possible cause is the presence of a greater degree of chronic inflammation in these patients. In patients with a GRA < 2, the degree of glomerulations showed no significant improvement after BoNT-A injections, in contrast to those with a GRA ≥ 2. Glomerulations in IC/BPS are associated with greater chronic inflammation and increased urothelial apoptosis (11). Patients who did not have significantly improved glomerulations after treatment might have less clinical improvement.

The characteristic cystoscopic findings of bladder ulcers indicate that localized bladder inflammation and unhealthy mucosa are present. Increased lymphocyte infiltration and abundant mast cells, eosinophils, and granulation tissues form a chronic inflammatory complex. Unless these chronic inflammatory lesions are ablated, the bladder pain can hardly be eradicated by BoNT-A injections alone. Ulcer type IC/BPS seems best treated with ablation rather than BoNT-A.

Patients with ulcer IC/BPS had mucosal ulceration, hemorrhage, granulation tissue, intense inflammatory infiltrates, elevated mast cell counts, and perineural infiltrates, whereas patients with non-ulcerous disease had a relatively mild mucosal defect and inflammatory response (36). Epidermal growth factor was significantly higher in patients with non-ulcer than ulcer IC/BPS (37). The clinical characteristics of ulcer IC/BPS in our study were intractable bladder pain, which was not related to bladder distention, in addition to the usual presenting symptoms such as frequency, urgency, and nocturia. The bladder pain elicited by the KCl test in ulcer IC/BPS was also more intense than in non-ulcer IC/BPS. Therefore, if a patient who had been diagnosed with IC/BPS had persistent bladder pain despite multiple medications or intravesical treatments, cystoscopy without anesthesia should be performed to rule out any bladder ulcers (8).

Many different treatments have been used to treat ulcer IC/PBS including cystectomy or partial cystectomy (38), cystoscopic YAG laser ablation of Hunner's ulcers (39), steroid therapy (40), submucosal injection of triamcinolone (41), and hyperbaric oxygen therapy (42,43). Despite these treatments, a cure for ulcer IC/PBS remains elusive. Additionally, repeated intravesical BoNT-A injections did not benefit patients with ulcer IC/BPS in our study. On the contrary, simple electrofulgaration using an ordinary transurethral resectoscope to cauterize the bladder ulcers immediately relieved bladder pain. Although symptoms recurred in some patients with ulcer IC/BPS, repeated electrofulgaration was still effective for symptom relief.

Conclusion

Repeated intravesical BoNT-A injections provided effective treatment outcomes in half of patients with non-ulcer IC/BPS, but did not benefit patients with ulcer IC/BPS. Ulcer type IC/BPS should be treated differently than non-ulcer IC/BPS.

References

1. Hanno P. Interstitial cystitis and related diseases. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ (eds). *Campbell's Urology*. 7th ed. WB Saunders, Co., Philadelphia, PA, 1998, pp 631-662.
2. Nigro DA, Wein AJ, Foy M, Parsons CL, Williams M, Nyberg LM Jr, Landis JR, Cook YL, Simon LJ. Association among cystoscopic and urodynamic findings for women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. *Urology* 1997; 49:86-92.
3. Hunner GL. A rare type of bladder ulcer in women: Report of cases. *Tans South Surg Gynecol Assoc* 1915; 27:247-292.
4. Nickle JC. Interstitial cystitis: A chronic pelvic pain syndrome. *Med Clin North Am* 2004; 88:467-481.
5. Denson MA, Griebling TL, Cohen MB, Kreder KJ. Comparison of cystoscopic and histological findings in patients with suspected interstitial cystitis. *J Urol* 2000; 164:1908-1911.
6. Koziol JA, Adams HP, Frutas A. Discrimination between the ulcerous and the nonulcerous forms of interstitial cystitis by noninvasive findings. *J Urol* 1996; 155:87-90.
7. Tomaszewski JE, Landi JR, Russack V, Williams TM, Wang LP, Hardy C, Brensinger C, Matthews YL, Abele ST, Kusek JW, Nyberg LM; Interstitial Cystitis Database Study Group. Biopsy features are associated with primary symptoms in interstitial cystitis: Results from the interstitial cystitis database study. *Urology* 2001; 57:67-81.
8. Braunstein R, Shapiro E, Kaye J, Moldwin R. The role of cystoscopy in the diagnosis of Hunner's ulcer disease. *J Urol* 2008; 180:1383-1386.
9. Tyagi P, Killinger K, Tyagi V, Nirmal J, Chancellor M, Peters KM. Urinary chemokines as non-invasive predictors of ulcerative interstitial cystitis. *J Urol* 2012; 187:2243-2248.
10. Hanno PM, Sant GR. Clinical highlights of the national Institute of Diabetes and Digestive and Kidney Diseases/Interstitial Cystitis Association scientific conference on interstitial cystitis. *Urology* 2001; 57:2-6.
11. Shie JH, Kuo HC. Higher levels of cell apoptosis and abnormal E-cadherin expression in the urothelium are associated with inflammation in patients with interstitial cystitis/painful bladder syndrome. *BJU Int* 2011; 108:E136-E141.
12. Brady CM, Apostolidis A, Harper M, Yiangou Y, Beckett A, Jacques TS, Freeman A, Scaravilli F, Fowler CJ, Anand P. Parallel changes in bladder suburothelial vanilloid receptor TRPV1 and pan-neuronal marker PGP9.5 immunoreactivity in patients with neurogenic detrusor overactivity after intravesical

resiniferatoxin treatment. *BJU Int* 2004; 93:770-776.

13. Cockayne DA, Hamilton SG, Zhu OM, Dunn PM, Zhong Y, Novakovic S, Malmberg AB, Cain G, Berson A, Kassotakis L, Hedley L, Lachnit WG, Burnstock G, McMahon SB, Ford AP. Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X3-deficient mice. *Nature* 2000; 407:1011-1015.
14. Chuang YC, Yoshimura N, Huang CC, Chiang PH, Chancellor MB. Intravesical botulinum toxin A administration produces analgesia against acetic acid induced bladder pain response in rats. *J Urol* 2004; 172:1529-1532.
15. Giannantoni A, Di Stasi SM, Nardicchi V, Zucchi A, Macchioni L, Bini V, Goracci G, Porena M. Botulinum-A toxin injections into the detrusor muscle decrease nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity. *J Urol* 2006; 175:2341-2344.
16. 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; 45:987-993.
17. Rapp DE, Turk KW, Bales GT, Cook SP. Botulinum toxin type a inhibits calcitonin gene-related peptide release from isolated rat bladder. *J Urol* 2006; 175:1138-1142.
18 Cayan S, Coskun B, Bozlu M, Acar D, Akbay E, Ulusoy E. Botulinum toxin type A may improve bladder function in a rat chemical cystitis model. *Urol Res* 2003; 30:399-404.
19. Steers WD, Tuttle JB. Mechanisms of disease: The role of nerve growth factor in the pathophysiology of bladder disorders. *Nat Clin Pract Urol* 2006; 3:101-110.
20. Apostolidis A, Papat R, Yiangou Y, Cockayne D, Ford AP, Davis JB, Dasgupta P, Fowler CJ, Anand P. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injection of botulinum A toxin for human detrusor overactivity. *J Urol* 2005; 173:977-983.
21. Reitz A, Stöhrer M, Kramer G, Del Popolo G, Chartier-Kastler E, Pannek J, Burgdörfer H, Göcking K, Madersbacher H, Schumacher S, Richter R, von Tobel J, Schurch B. European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. *Eur Urol* 2004; 45:510-515.
22. Smith CP, Radziszewski P, Borkowski A, Somogyi GT, Boone TB, Chancellor MB. Botulinum toxin A has antinociceptive effects in treating interstitial cystitis. *Urology* 2004; 64:871-875.
23. Giannantoni A, Costantini E, Di Stasi SM, Tascini MC, Bini V, Porena M. Botulinum A toxin intravesical injections in the treatment of painful bladder syndrome: A pilot study. *Eur Urol* 2006; 49:704-709.
24. Kuo HC. Preliminary results of suburothelial injection of botulinum A toxin in the treatment of chronic interstitial cystitis. *Urol Int* 2005; 75:170-174.
25. Cui M, Aoki KR. Botulinum toxin type A (BTX-A) reduces inflammatory pain in the rat formalin model. *Cephalalgia* 2000; 20:414-418.
26. Giannantoni A, Porena M, Costantini E, Zucchi A, Mearini L, Mearini E. Botulinum A toxin intravesical injection in patients with painful bladder syndrome: 1-year followup. *J Urol* 2008; 179:1031-1034.
27. Kuo HC. Repeated onabotulinumtoxin-A injections provide better results than single injection in treatment of painful bladder syndrome. *Pain Physician* 2013; 16:E15-E23.
28. Homma Y, Ueda T, Tomoe H, Lin AT, Kuo HC, Lee MH, Lee JG, Kim DY, Lee KS; Interstitial cystitis guideline committee. Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. *Int J Urol* 2009; 16:597-615.
29. O'Leary MP, Sant GR, Fowler FJ Jr, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. *Urology* 1997; 49:58-63.
30. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A; Standardisation Subcommittee of the International Continence Society. The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; 21:167-178.
31. Parsons CL. The potassium sensitivity test: A new gold standard for diagnosing and understanding the pathophysiology of interstitial cystitis. *J Urol* 2009; 182:432-434.
32. Nickel JC, Barkin J, Forrest J, Mosbaugh PG, Hernandez-Graulau J, Kaufman D, Lloyd K, Evans RJ, Parsons CL, Atkinson LE; Elmiron Study Group. Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. *Urology* 2005; 65:654-658.
33. 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; 104:657-661.
34. Liu HT, Kuo HC. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. *Urology* 2007; 70:463-468.
35. Pinto R, Lopes T, Frias B, Silva A, Silva JA, Silva CM, Cruz C, Cruz F, Dinis P. Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/interstitial cystitis. *Eur Urol* 2010; 58:360-365.
36. Johansson SL, Fall M. Clinical features and spectrum of light microscopic changes in interstitial cystitis. *J Urol* 1990; 143:1118-1124.
37. Zhang CO, Li ZL, Kong CZ. APF, HB-EGF, and EGF biomarkers in patients with ulcerative vs. non-ulcerative interstitial cystitis. *BMC Urol* 2005; 5:7.
38. Rössberger J, Fall M, Peeker R. Long-term results of reconstructive surgery in patients with bladder pain syndrome/interstitial cystitis: Subtyping is imperative. *Urology* 2007; 70:638-642.
39. Rofeim O, Hom D, Freid RM, Moldwin RM. Use of the neodymium: YAG laser for interstitial cystitis: A prospective study. *J Urol* 2001; 166:134-136.
40. Soucy F, Grégoire M. Efficacy of prednisone for severe refractory ulcerative interstitial cystitis. *J Urol* 2005; 173:841-843.
41. Cox M, Klutke JJ, Klutke CG. Assessment of patient outcomes following submucosal injection of triamcinolone for treatment of Hunner's ulcer subtype interstitial cystitis. *Can J Urol* 2009; 16:4536-4540.
42. Tanaka T, Kawashima H, Makino T, Kamikawa S, Kato N, Nakatani T. Hyperbaric oxygen therapy for interstitial cystitis resistant to conventional treatments. *Int J Urol* 2007; 14:563-565.
43. Tanaka T, Nitta Y, Morimoto K, Nishikawa N, Nishihara C, Tamada S, Kawashima H, Nakatani T. Hyperbaric oxygen therapy for painful bladder syndrome/interstitial cystitis resistant to conventional treatments: Long-term results of a case series in Japan. *BMC Urol* 2011; 11:11.