Evaluation of Therapeutic Effect of Intratrigonal Injection of AbobotulinumtoxinA(Dysport) and Hydrodistention in Refractory Interstitial Cystitis /Bladder Pain Syndrome

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Purpose: There are two brands of BotulinumtoxinA(BTXA) that are commonly used in the treatment of Lower Urinary Tract Disease: OnabotolinumtoxinA(Ona-BTXA) and AbobotulinumtoxinA (Abo-BTXA). The present study was conducted to assess the potential therapeutic and adverse effects of Abo-BTXA or Dysport for interstitial cystitis/bladder pain syndrome (IC/BPS).

Materials and Methods: Twenty-two out of 52 women diagnosed with IC/BPS who were refractory or had a low response to oral treatments of IC/BPS after 6 months, were included in the study. The end-point was O'Leary-Sant Score (OSS) including "symptoms" and "problem" indexes (ICSI and ICPI respectively) assessment after 1,3and 6 months after Abo-BTXA injection. Each patient underwent cystoscopy and immediately after hydrodistention received intratrigonal injections of 300 IU of Abo-BTXA (Dysport®) in 30 sites. The effect and side effects of this treatment over time have been investigated. Complications including high post void residual urine (PVR), bladder rupture, and urinary tract infections (UTI) were also assessed.

Results: The mean age of patients was 46.2 ± 13.7 years and the median OSS was 27.8 ± 5.8.: After a single injection ICSI, ICPI, and total OSS significantly reduced in 1, 3, and 6 months follow up; rate of decreased total OSS was 39.5%, 36%, 18%, respectively. Its effect lasted up to six months and started to decrease after 1 month (p-value < 0.05). Complications included urinary retention (PVR > 200ml), bladder rupture, and UTI in 13.5%, 4.3%, and 18% of the patients, respectively.

Conclusion: Intravesical injection of 300IU Abo-BTX(Dysport) could be a useful approach for the treatment of patients with refractory IC/BPS in a period of six months.

Keywords: AbobotilinumtoxinA; bladder pain syndrome; Botulinum toxin ; Dysport; refractory interstitial cystitis; intravesicle injection

INTRODUCTION

Interstitial cystitis/bladder pain syndrome (IC/BPS) is characterized by symptoms like urinary urgency, urinary frequency, and nocturia in middle-aged women. Due to the lack of a universal concurrence of the diagnostic criteria, it is not possible to estimate the prevalence of IC/BPS precisely; however, it has been reported that between 2.7% and 6.5% of the women in the United States suffer from IC.[1] In addition, based on the O'Leary-Sant Score (OSS) questionnaire prevalence of IC/BPS among women has been reported to be 265 in 100,000 in Japan, 450 in 100,000 in Finland, and 306 in 100,00 in Austria[2-4]

Although patients usually suffer from dysuria and have urinary urgency in the absence of UTI, their conditions rarely (14%) related to urodynamic detrusor overactivity.[5] The exact pathophysiology of IC/BPS is unclear; however, some possible underlying factors are proposed to explain the etiology of the disease including changes in urothelial permeability, mast cell activation, and abnormal sensory nerve stimulation especially in bladder afferent pathways. The interesting point in the last hypothesis is that it includes all other mechanisms and provides a comprehensive explanation; i.e., neuritis.[6] According to this hypothesis, some of the suggested treatments focused on intravesical therapy; e.g., hydraulic distension of the bladder, intravesical instillation of DMSO, or chondroitin sulfate.[1]

Considering the probable neuritis origin of IC/BPS, a neuromodulation procedure that directly manipulates the vesical nerves can be a reasonable treatment[7]

Intravesical injection of Botulinum toxin type A (BTXA) was suggested as an overactive bladder (OAB) and IC/BPS treatment for the first time 15 years ago.[8] Many studies approved its positive effect in, improv-

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Table 1. Demographic information and medical records.

Demographic variable	Details
Age(year),mean ±SD	46.24 ± 13.791
Duration of symptoms(m),mean ± SD	111.73 ± 113.653
Marriage, N (%)	
Married	20(90.9)
Single	2(9.1)
Pelvic surgery N (%)	
C/S	5(22.72)
Hysterectomy	4(18.18)
Tube ligation	3(13.63)
Cystocele repair	2(9.09)
Perianal abscess drainage	1 (4.54)
None	9(40.9)
NVD N (%)	
None	9(40.9)
2	5(22.72)
4	4(18.18)
3	2(9.09)
5	1(4.54)
1	1(4.54)
Comorbidity N (%)	
None	12(54.54)
IBS	4(18.18)
Anemia	2(9.09)
Discopathy	2(9.09)
PUD	1(4.54)
HTN	1(4.54)
IBD	1(4.54)
Nephrolithiasis	1(4.54)
Hypothyroidism	1(4.54)
UTI, N (%)	10(45.5)
Nervosas	18(81.8)

ing bladder sensory symptom and pain in association with reduction of the level of urinary NGF levels.[9-11], and interestingly some other studies reported that the response in patients with IC/PBS depends on the phenotype of the disease, i.e., ulcerative or non-ulcerative.[12] To assess the effects of Abo-BTXA on IC/BPS symptoms according to OSS questionnaire including urinary urgency, urinary frequency, nocturia, and suprapubic pain, patient's quality of life, and potential complications of this method, we designed the present study to compare the symptoms and complications related to IC/BPS in female patients before and after intravesical injection of Abo-BTXA. To our knowledge, there is little evidence about intravesical injection effects of Abo-BTXA versus Ona-BTXA (BOTOX).

MATERIALS AND METHODS

Patients

The study was designed as a single-center prospective interventional quasi-experimental study and was conducted between November 2013 and October 2017 in our center. Ethical and technical approval was obtained from the Urology and Transplantation Research Center of Isfahan University of Medical Sciences. The participants of the present study included women 18- 80 years old examined at the outpatient clinics affiliated to Isfahan University of Medical Sciences. The participants were diagnosed with IC/BPS based on ICDB criteria and their symptoms lasted at least 4 months.[13] All these patients received different medical treatments approved in the AUA guideline of interstitial cystitis for 1 year.[14] Other inclusion criteria were a lack of response to the medical treatment or recurrence of symptoms after at least 6 months. All participants were informed about the therapeutic effects and complications of the treatment including generalized muscle weakness, difficulties in urination, transient urinary retention, clean intermittent catheterization (CIC), and UTI. Informed consent was obtained from all participants.

Exclusion criteria included any gross pathology in urinary tract, active UTI (as documented by urine culture), pregnancy, pelvic radiation, endometriosis, bladder cancer, pelvic reconstructive surgery, anti-incontinence surgery, and any contraindications of BTXA injection including a known allergy to Dysport, a history of myasthenia gravis, amyotrophic lateral sclerosis or injection of the toxin for any reason in previous 6 months.

Procedures and technique

Among 52 women diagnosed with IC/BPS, 22 patients who did not respond to conventional medication treatments of IC/BPS according to 2017 EUA guidelines, developed side effects, or who refused the treatment were enrolled in the study. All patients were admitted to the hospital on the day of the procedure. IC/BPS symptom and problem indexes were evaluated before the treatment by the OSS questionnaire. The internal consistency of the indices is precisely enhanced by Cronbach's alpha, which exceeded 0.85 for the symptom index, and 0.90 for the problem index.[15]

All patients received 1g ceftriaxone before the procedure and underwent regional or general anesthesia depending on the choice of the anesthesiologist. injection technique and type of toxin are still controversial issues. We used Dysport because it is the only type of BTXA approved by the Ministry of Health in Iran. In addition, there are few studies about the intravesical injection of Abo-BTXA for the treatment of IC/PBS; therefore, the result of evaluating this type of botulinum in this group of women would be interesting. All patients received 300UI of Dysport (Abobotulinum toxin A, Ipsen Biopharmaceuticals, Pharma, Germany, DYS-US-001865). After cystoscopy and bladder hydrodistention, each 300U Dysport vial was diluted with 3 ml of normal saline (the concentration was 100IU/ml). The amount of toxin is controversial and depends on the type of BTXA and indications. We used the lowest doses of Abo-BTXA (300 IU) which has been utilized intravesical successfully in adult patients.

Dysport 300U in 3 cc saline was injected as 30 trigonal and bladder base of 0.1 ml (every lateral side of trigon triangle 6-8 injections and inside and outside of base or inter orifice ridge of trigon at suburothelium 14-18 injections) using 21GA needle (10 IU/site). We chose intratrigonal injection because trigon contains a prominent parasympathetic plexus, the most concentrated site of sensory and peripheral afferent nerve ending in the bladder. Foley catheter was removed after 24 hours. Patients were discharged during the first postoperative day if PVR was less than 200 ml. Patients had been recommended and taught timed voiding. Ciprofloxacin 500mg for 5 days was also prescribed for them. Patients were in a stable condition regarding their LUTS before intervention; therefore, the change of their OSS was considered to result from intravesical treatment. Patients were examined at 1, 3, and 6 months after the injection. The primary goal of the study was assessing the changes of OSS, the voiding diary, brief symptoms inventory, the occurrence of UTI, CIC, and urethra or bladder perforation. Finally, the results of the OSS and voiding diary were compared between pre and post intravesical injection.

The therapeutic outcome was assessed using the OSS

Table 2. The changes of Parameters at baseline, 3 and 6 months after single BoNT-A injection

Parametrs	Baseline	1 Months	3 Months	6 Months	*p*-value
OSS	27.863 ± 5.808	17.0 ± 9.304	17.636 ± 9.348	22.636 ± 8.742	< 0/001
Symptom	14.818 ± 3.800	8.090 ± 5.681	8.863±5.453	12.136 ± 5.148	< 0/001
Problem index	13.045 ± 2.192	8.318 ± 4.156	8.681±4.133	10.636 ± 3.885	< 0/001
Urgency (s1)	4.22 ± 1.06	2.40 ± 1.62	2.50 ± 1.50	3.27 ± 1.57	< 0/001
Frequency (s2)	3.90 ± 1.37	2.04 ± 1.49	2.22 ± 1.44	3.04 ± 1.52	< 0/001
Nocturia(s3)	3.00 ± 1.57	2.04 ± 1.98	2.09 ± 1.94	2.68 ± 1.75	< 0/001
Suprapubic pain/dysuria (s4)	3.68 ± 1.24	2.04 ± 1.13	2.18 ± 1.29	2.86 ± 1.32	< 0/001

changes, every patient's OSS was compared with baseline: women with more than 10% improved total OSS after treatment were considered to have recovery response, otherwise, patients were considered "non-responder". Statistical analysis was performed using SPSS version 25.0 and the level of significance was considered 0.05. Investigation of changes in OSS and symptom indices mean over time were performed by repeated measures analysis of variance (ANOVA) to examine the impact of the intervention over time. The post-hoc test is then performed to find a significant difference at times. In addition, tests of within-subject's contrasts were performed to examine the shape of the mean changes over time.

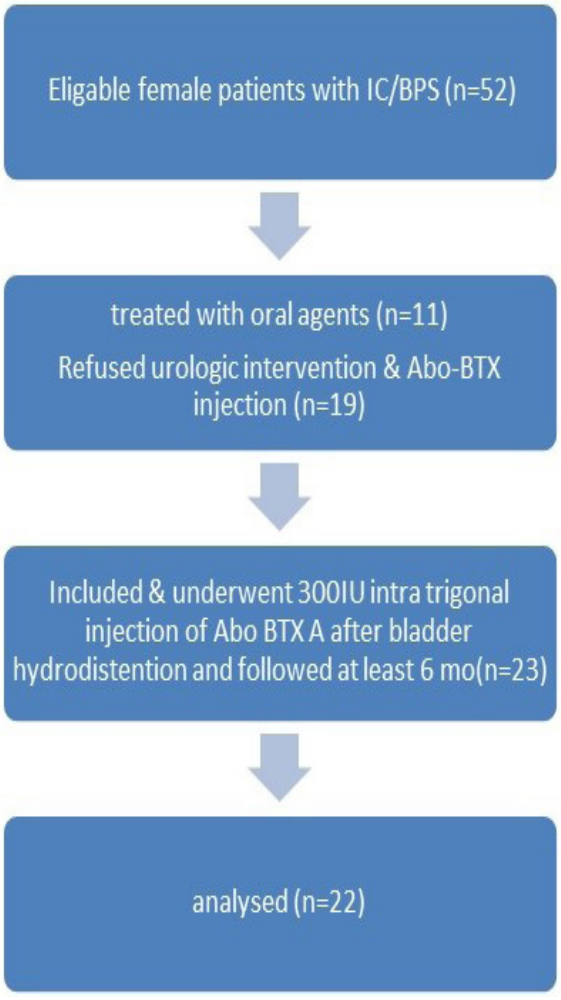

Figure 1. Flow diagram of enrollment of patients to the study.

RESULTS

Twenty-two out of 52 women diagnosed with BPS enrolled in the interventional phase of the study. The steps are shown in Figure 1.

The patients aged from 24 to 74 years with a mean of 46.24 ± 13. 71 years. The duration of symptoms was from 6 to 396 months and its mean was 111.73±113.653 months. The majority of patients (90.9%) were married. The most common pelvic surgery was a cesarean section (5 patients, 22.7%), which may be a predisposing factor for PBS. More than half of the patients did not have any comorbidities but the most common one among those who had was IBS (4 patients, 18.18%). Positive urine culture in a patient's medical records was considered as UTI. According to this index, 12 patients (54.5%) did not have any infection and 10 (45.5%) had at least one episode of UTI. Demographic information and medical records of patients are detailed in **Table 1**. The results (**Table 2**) show a total mean of 27.86 ± 5.808 for total OSS score before the treatment, the mean rate of its was reduced to 38.99% after 1 month, 36.72% after 3 months, and 18.78% after 6 months (p-value< 0.001). We obtained a mean of 14.82 ± 3.800 for the ICSI before the treatment. As presented in Table 2, the mean symptom index reduced to 45.38%, 40.18%, and 18.1% after 1, 3, and 6 months, respectively (*p*-value< 0.001). Each of the symptoms evaluated by OSS questionnaire including urgency, frequency, nocturia, and suprapubic pain/dysuria had a significant reduction (all *p* values: < 0.001). The ICPI mean was 13.04 ± 2.192 before the treatment that reduced to 36.28%, 33.44%, and 18.49% after 1, 3, and 6 months, respectively(all *p* values: < 0.001).

Willing to retreatment was taken into account when the patient asked for the re-injection again. Seven patients (31.8%) were willing to receive the treatment again while 15 were not, which of these 15, one patient was completely cured and two experienced a major decrease in their symptoms. Only 4 patients did not have a record of nervosis, such as depression, anxiety, chronic tension headache.

Complications were classified into two major categories: the systemic adverse effects of Dysport and Vesicle formation after surgery. The systemic adverse effects of Dysport (including weakness in all of the muscles in the body, double vision, difficulty breathing, or swallowing) did not happen in any of the patients. The bladder complication happened in 4 patients. In one of them, "bladder rupture" was developed due to neglected urinary retention, which was completely restored. The patient administered an indwelling catheter for 7 days and was advised to take CIC for 5 days. This patient finally had completely normal urination and was one of the patients who returned after 1 year for retreat-

ment. Voiding dysfunction and overflow incontinence due to impaired detrusor contractility happened in 3 patients who needed CIC for 1-2 weeks after the intervention. UTI developed in 5 of the patients during the first 6-month follow-up.

DISCUSSION

Our results suggest that a dose of 300 IU Abo-BTXA results in the improvement of QOL and a decrease in irritative symptoms in IC/BPS patients similar to the effect of 100 IU of Botox.[16,17] OSS and QOL improved significantly: The peak effect of the treatment was about 1 month (40% reduction rate in OSS) but it could last for six months (20% reduction rate in OSS). Tests of contrasts showed the decline over the six-month was non-linear. The sharpest decline was observed in the first month, followed by a trend of up to three months and rising in six months. Although various botulinum toxin preparations and serotypes have a similar mechanism, which is blocking neurotransmitter release[18], a comparison of Ona-BTXA (Botox) and Abo-BTXA (Dysport) showed that Botox tends to have higher efficacy, longer duration, and higher frequency of adverse effects in the treatment of detrusor overactivity.[19]

Our results show that urine urgency has the highest frequency among patients but the one that makes the biggest effect on the quality of life is suprapubic pain or dysuria. Based on the literature, Abo-BTXA is a chemical neuromodulator affecting the sensory and pain nerves by inhibition of neurotransmitter release in neuromuscular junctions, especially in cholinergic terminals[20] and reduction of some sensory receptors like P2X3 and TRPV1[21], and capsaicin expression in axons. In addition, it has central desensitization effects by a decrease in uptake of substance P in CNS.[22] The efficacy of Abo-BTXA in our groups of patients was less than expected compared to Botox used in another similar study.[22]

Our results were different from the results obtained by Kuo HC et al.[23] One possible explanation is the use of different questionnaires - OSS in our study versus VAS in Kuo's study. Another explanation is that BOTOX is more effective than Dysport in blocking of sensory nerve endings.

It is expected that patients referred for LUTS treatment who have a high urinary score on UPOINT show a better response to intravesical injection. Therefore, estimation of the patient's UPOINT score before treatment helps in the identification and selection of those who have a high score on urinary or organ-specific domain, which leads to a better rate of successful treatment.

BTXA has been reported to have an antinociceptive effect on IC/BPS.[8] In addition, other studies approved the positive effect of BTXA on decreasing the IC/BPS symptoms[9,23,24] and increasing the bladder capacity and urodynamic parameters.[10,25,26] Some studies reported that the injection of Abo-BTXA followed by hydrodistention can reduce bladder pain.[27,28] In contrast, other studies that used the injection of BTXA without hydrodistention supported the efficacy of injecting BTXA without hydrodistention.[11]

We decided to use hydrodistention before Dysport injection according to the theory that sensory nerve ending necrosis due to hydrodistention may increase toxin absorption and efficacy. It has been reported that this treatment can reduce the irritative symptoms and increase the bladder capacity only in the non-ulcer type of IC/BPS, and there is no improvement in symptoms or urodynamic in ulcer type of the disease.[12] In a cohort study by Pinto et al. (2014), it was suggested that there is no connection between the presence and absence of "Hunner's ulcer" and response to Ona-BTXA.[29] Studies that injected Botox multiple times reported that the therapeutic effects of multiple injections are persistent.[30] In addition in another study, it was suggested that multiple injections provide better outcomes compared to a single injection.[31] There are other studies including a multi-center randomized double-blind study that did not obtain any positive effects - reducing or curing the symptoms - after treatment.[32,33] There is no study about the therapeutic and adverse effects of Abo-BTXA or Dysport on IC/BPS in Iran; therefore, this study can be a guide for more sophisticated researches in the future. The follow-up period was 6 months in this study and we observed that the therapeutic effects reduced over time, however, the effects remained after the 6-month follow-up. In one study, the authors reported that the therapeutic effects can persist more than 50% after 9 months.[26] Since we excluded any patient with contraindications to BTXA including patients with Gillen Barre, patients using aminoglycoside, or those with any history of Dysport hypersensitivity, we did not observe any significant systemic adverse effects related to Dysport. It is noteworthy that no other study reported such adverse effects.[20] We had two major bladder-related complications, one was bladder rupture and the other was prolonged urinary retention (> 4 weeks) which was reported in other studies [10,30,34] and could be related to the dosage of the toxin. In a study that used 100 IU Botox, no adverse effects were reported.[26] Extraperitoneal bladder rupture was observed in one of the patients 24 hours after injection due to the neglected urinary retention. Although the rupture was successfully restored and the patient did not experience any difficulties and returned for retreatment the next year, it is a serious issue that should be investigated further. Certainly, it should be kept in mind that the rupture of the bladder is a limitation on the scientific basis of hydrodistention[34] and urinary retention, especially in thin bladder wall of BPS patients. We advised routine control of PVR in all the patients because bladder sensation after Abo-BTXA (Dysport) injection is not reliable. Post-surgery UTI is one of the complications reported in some studies.[10,35] We also observed acute cystitis in 4 (18%) patients during the 6-month follow-up. It may be due to impaired contractility and high PVR after Dysport injection. The response rate to intravesical injection of Dysport was less than 40%, the matter is why it fails in some of patients and how we must improve patient selection for intravesical treatment? Because of heterogeneous nature of PBS, detailed clinical phenotype using UPOINT (urinary, psychosocial, organ specific, infection, neurological/systemic / tenderness) system may guide therapy for this organ specific and urinary treatment.[36] IC/BPS women with less domains of UPOINT may be have a better response to treatment.[37] Due to financial limitations we designed the study without a control group. In addition, we did not include urodynamic test and only asked if patients suffered from voiding dysfunction or urge incontinence. Therefore, further investigations using UPOINT, applying other assessment methods and having a control group provide additional

information about the treatment options of the patients.

CONCLUSIONS

Injection of 300 IU Abo-BTX A has shown to improve symptoms and QOL in half of the women with refractory IC/ PBS. In addition, there was a low risk of retention and morbid complications in the patients.

CONFLICT OF INTEREST

None declared.

APPENDIX:

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