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CLINICAL ARTICLE

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Sexual dysfunction in women with interstitial cystitis/bladder pain syndrome: Do onabotulinum toxin-A injections improve sexual function?

Murat Topcuoglu MD[1] | **Murat Can Karaburun MD**[2] | **Arif İbiş MD**[2] | **Mehmet İlker Gokce**[2] | **Evren Süer**[2] | **Omer Gülpinar**[2]

[1]Department of Urology, Alaaddin Keykubat University Education and Research Hospital, Denizli, Turkey

[2]Department of Urology, Ankara University School of Medicine, Ankara, Turkey

Correspondence
Omer Gülpinar, Department of Urology, Ankara University School of Medicine, Adnan Saygun Caddesi, Altindag, Ankara 06480, Turkey.
Email: ogulpinar@ankara.edu.tr

Abstract

Introduction: Interstitial cystitis/bladder pain syndrome (IC/BPS) has a negative impact on female sexual function. We aimed to evaluate the effect of intravesical botulinum toxin-A (BTX-A) injection on the improvement of sexual dysfunction and urinary symptoms using the multi-domain female sexual function Index (FSFI), interstitial cystitis symptom index (ICSI), and interstitial cystitis problem index (ICPI).

Material and Method: The data of the 23 patients (study group) who received intravesical BTX-A with the diagnosis of IC/BPS were reviewed. Twenty-three age-matched healthy, sexually active women were determined as the control group. Patients received 100 U BTX-A submucosally injections, including the trigone. One hundred units of BTX-A were diluted to 20 cc 0.9% saline, and 1 cc was then applied submucosally on 20 different points of the bladder wall (5 U/1 mL per site). The study group was asked to fill out FSFI, ICSI, and ICPI, as well as the visual analog scale (VAS) and bladder diary before and 3 months after the treatment. Patients in the control group completed the same questionnaires once. The pre- and post-treatment questionnaire scores were compared in the study group. The study group's data were also compared to the control group.

Results: Compared to the pretreatment period, the study group showed statistically significant improvement in the total FSFI score and each domain of the FSFI after BTX-A injection. The mean total FSFI score and three domains of FSFI (desire, lubrication, pain) reached to the score of the control group following BTX-A injection. Statistically significant improvements were also shown in scores of ICSI, ICPI, and VAS. ($p < 0.05$).

Conclusion: IC/BPS is associated with a very high incidence of sexual dysfunction. Intravesical BTX-A injection may provide significant improvement in sexual dysfunction in women with IC/BPS.

KEYWORDS
bladder pain syndrome, botulinum toxin, interstitial cystitis, sexual dysfunciton, women

1 | INTRODUCTION

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic, debilitating bladder disease that results in poor quality of life with sexual dysfunction, sleep disorders, depression, anxiety, and stress.[1] In previous studies, IC/BPS was found to have a prevalence ranging from 0.45% to 12.6%, had a significant negative impact on quality of life, and could lead to depression, anxiety, insomnia, fatigue, decreased work productivity, dyspareunia, and other sex-related problems.[2–5] While the main symptom is an increase in chronic pain and discomfort associated with bladder filling, IC/BPS is also significantly associated with severe health consequences that can lead to a reduced quality of life.[6] Meanwhile, data from a telephone screening study of 985 IC/BPS patients reported that 90% of IC/BPS patients reported sexual dysfunction (SD), which is significantly higher than the general population (43%).[7] In a study with a large number of cases, Zaslau et al.[8] reported significant SDs in all IC/BPS patients as compared to a control group of healthy volunteers. The SD in IC/BPS women is broad and includes dyspareunia, hypoactive desire, insufficient lubrication, and orgasmic difficulties.[9] Pain is the most common cause of avoidance of sexual activity in women with IC/BPS.[10] Improvement of sexual function in women with IC/BPS is an important factor in improving patient satisfaction with treatment.[11] Furthermore, sexuality is a very important part of general health in women and is affected by anatomical, physiological, medical, and social factors.[12] Although there are very limited data about the improvements in the sexual function in women with IC/BPS following various treatments, including oral and intravesical instillations, the current literature has not investigated the improvement in SD following intravesical injection of botulinum toxin-A (BTX-A)[13,14] BTX-A was first used as an intravesical injection for the treatment of refractory IC/BPS in 2004 and recommended by the American Urological Association (AUA) as a fourth-line therapy.[15,16] The European Association of Urology (EAU) guideline gives a grade C recommendation for the use of intravesical BTX-A as a single treatment, as well as other guidelines recommend it as an option after the failure of other therapies in patients who are well-counseled about the risks (such as the need for a clean intermittent self-catheterization).[17]

Favorable outcomes in terms of improvement of sexual dysfunction have been reported in women who underwent intravesical installation of sodium hyaluronate and sodium chondroitin sulfate, and oral pentosan polysulfate (PPS) 300 mg/day.[13,14] In addition, similar improvements in sexual dysfunction following BTX-A injection in neurogenic and non-neurogenic OAB syndrome were reported in previous studies. These results in the current literature encouraged us to show the effect of BTX-A injection on sexual function in IC/BPS patients.[18,19] We focused on the importance of sexual function in women with IC/BPS and aimed to evaluate the impact of intravesical injection of BTX-A. The primary endpoint was the assessment of improvement in SD, while the secondary endpoint was the change in pain and urinary symptoms after the BTX-A injection. For this purpose, the multi-domain female sexual function index (FSFI), interstitial cystitis symptom index (ICSI), and interstitial cystitis problem index (ICPI) were used. We aimed to demonstrate the effects of intravesical injection of BTX-A on SD through the improvement in pain status and urinary symptoms.

2 | MATERIAL AND METHODS

This study was conducted according to the ethical standards laid down by the 1964 Declaration of Helsinki and its later amendments and approved by the local ethics committee of our institute (No. İ01-46-22). The data of the 23 patients who were diagnosed with refractory IC/BPS and received intravesical BTX-A injections between January 2015 and December 2019 were prospectively collected, and the data were analyzed retrospectively in this single-center study. IC/BPS was diagnosed according to the definition of "An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable cause."[16] The study group was named "Group 1." Subsequently, 23 age-matched healthy sexually active women without any lower urinary tract symptoms were determined as the control group which was named as Group 2. This group consisted of patients who underwent routine gynecological examinations and cervical smears in the outpatient clinic. Exclusion criteria's included previous intravesical BTX-A injection, pelvic organ prolapse stage III or IV, history of bladder tumors, chemical cystitis, tuberculous or radiation cystitis, urolithiasis, urological malignancy, bladder outlet obstruction, endometriosis, urethral diverticulum, current hematuria, any contraindication for urethral catheterization, any neurological or endocrine disorder, arrhythmia, poorly controlled hypertension, severe cardiopulmonary disease, renal or liver failure, previous pelvic radiotherapy or chemotherapy, pregnancy, breastfeeding, active sexually transmitted disease, current or frequent urinary tract infection (UTI) (more than twice in the last 6 months as documented by the urine cultures), and taking prophylactic antibiotics to

prevent UTI. As per our protocol, 23 patients who failed to respond to first- and second-line treatments, including intravesical instillation of chondroitin sulfate, heparin, and hyaluronic acid, were included in the study group. Written informed consent was obtained from all of the participants in the study. All patients in the study group received conservative first-line therapies and oral drugs for second-line therapy. Ten patients received PPS therapy, and 13 patients received amitriptyline or hydroxyzine as a second-line oral therapy, but none of these 23 patients achieved satisfactory results.

Seventeen patients from the study group received intravesical therapy as second-line intravesical therapy. Chondroitin sulfate, hyaluronic acid, and heparin were administered intravesically to 9, 5, and 3 of the 17 patients, respectively. Six patients in the study group were reluctant to receive any type of conventional intravesical instillation therapy, such as chondroitin sulfate, hyaluronic acid, and heparin. No patient in the study group received any type of third- and fourth-line therapy, such as fulguration, hydrodistension, and neuromodulation.

All patients in the study group were asked to fill out validated Turkish version of the FSFI and ICSI (range of 0–20) as well as the ICPI (range of 0–16) and visual analog scale (VAS) for pain assessment at the preoperative period and at the third month of intravesical injection.[20,21] The patients in the study group were asked to fill out a 3-day bladder diary (BD) preoperatively and at the third month postoperatively to assess functional bladder capacity and daytime and nocturnal urinary frequency. Patients in the control group were asked to fill out FSFI, ICSI, ICPI, VAS, and BD only once at the beginning of the study.

Subsequently, the surgical procedure was performed by a single surgeon. Here, 100 units of BTX-A were diluted to 20 cc 0.9% saline, and 1 cc was then applied submucosally on 20 different points of the bladder wall using a 25-gauge needle (5 U/1 mL per site). Patients received 100 U BTX-A submucosally injections, including the trigone. Patients had 5 injections into the trigone and 15 injections into the bladder wall.

All patients were discharged from the hospital on the first day of injection. At this point, the patients were warned that clean intermittent catheterization is required if deemed necessary. In the third week of surgery, uroflowmetry was performed, and postvoid residual volume was measured to rule out urinary retention. Finally, the mean scores of FSFI, ICSI, ICPI, VAS, and BD data at baseline and 3 months after the treatment were compared between the study and the control groups. The primary endpoint was the assessment of improvement in SD, while the secondary endpoint was the change in pain and urinary symptoms after the BTX-A injection.

2.1 | Statistical analysis

χ^2 and the Fisher exact tests were used to compare nominal variables between independent groups. Descriptive statistics are presented with frequency, percentage, mean, and SD values. To analyze the differences between the study group's pre- and postinjection data, a paired *t*-test analysis was used. An Independent sample *t*-test was used to determine the difference between the study group and the control group. The power and sample levels were calculated by using G*Power Version 3.1.7. The study can be adequately represented with a power of 80% with 46 participants. The effect size level of the study was set as 0.42 (0.10 as the small, 0.25 as the medium, and 0.40 as the large effect sizes).[22] A p value less than 0.05 is considered significant.

3 | RESULTS

The demographic characteristics of the patients in both groups are displayed in Table 1. Both groups were statistically similar in terms of mean age, parity, and percentage of postmenopausal patients, marital status, educational status, and comorbidities. In all, 65.2% of patients in the study and 69.5% of the patient in the control group were premenopausal women. The mean time between the onset of IC/BPS symptoms and BTX-A injection in the study group was 32 ± 5.6 (13–40) months. Significantly lower scores in all domains of FSFI except

TABLE 1 Baseline demographic characteristics of groups.

	Group 1[a]	Group 2[b]	*p* Value
Mean age (years)	46.8 ± 12.1	45.7 ± 10.2	0.134
Postmenopausal (*n*)	15 (65.2%)	16 (69.5%)	0.246
Mean parity (*n*)	2.1 ± 0.8	1.9 ± 0.7	0.234
Married (*n*)	22	23	0
Educational status			
İlliterate	3	2	
Primary	4	4	0.862
High School	9	8	
University	7	9	
Serious comorbidity	3	2	0.773

[a]Group 1: study group.
[b]Group 2: control group.

lubrication at the pretreatment period were shown in patients with IC/BPS compared to the control group. Dyspareunia was described by 17 patients (74%) in the study group compared to seven patients (30%) in the control group. In the third month of the surgery, 20 patients had increased FSFI scores, whereas three patients had decreased FSFI scores. The mean total FSFI score increased from 21.53 ± 7.02 to 28.34 ± 7.85 in the postoperative period as compared to the baseline in the study group, which was statistically significant (Table 2). Improvement in all domains of FSFI was statistically significant in the follow-up period compared to the baseline period. In addition, three domains of FSFI (desire, lubrication, and pain) in the study group were similar to those of the patients in the control group following intravesical BTX-A injection. (Table 3). Meanwhile, 20 of 23 patients showed improvement in ICSI and ICPI scores, while three patients showed no improvement at the postoperative assessment. ICSI and ICPI scores showed statistically significant improvement in the posttreatment period as compared to baseline scores. Eighteen patients had lower VAS scores, while one patient had a higher VAS score in the postoperative compared to the pretreatment period. There was no change in VAS scores in four patients. Preoperative assessment of the mean VAS score showed a significant decrease from 8.31 ± 1.45 to 6.52 ± 1.72 during he follow-up period.

Statistically significant improvements were also observed in parameters such as daytime frequency, nocturnal frequency, and mean voided volume following BTX-A injection (Table 4). Evaluation of adverse events showed that symptomatic UTI was encountered in two patients. Two patients described dysuria without any proven UTI. One patient had urinary retention and required clean intermittent catheterization for 12 weeks.

4 | DISCUSSION

This is the first study in the current literature to demonstrate the effect of intravesical BTX-A injection on SD, in patients with IC/BPS. We investigated the effect of intravesical BTX-A injection on the different domains of sexual function as the primary endpoint of the study. Here, the term "sexual health" is defined as a state of physical, emotional, mental, and social well-being in relation to sexuality by the World Health Organization (WHO). Meanwhile, female SD is defined as a condition that causes some degree of personal discomfort due to changes in desire, arousal, orgasm, and pain during sexual activity.[23] Previous studies have revealed a clear relationship between SD and lower

TABLE 2 Change in scores of questionnaires from baseline pretreatment period to postoperative period in the study group and in comparison to the control group.

	Group 1[a] preoperative scores (*n*: 23), *X* ± SD	Group 1[a] postoperative scores) (*n*: 23), *X* ± SD	Preoperative and postoperative comparison of Group 1 (*p* value)	Group-2[b] scores (*n*: 23), *X* ± SD	Preoperative scores of Group 1 versus Group 2	Postoperative scores of Group 1 versus Group 2
FSFI	21.53 ± 7.02	28.34 ± 7.85	0.015	30.41 ± 8.32	0.029	0.234
ICSI	15.43 ± 3,06	12.45 ± 3.62	0.023	8.45 ± 2.20	0.013	0.027
ICPI	12.26 ± 2.59	9.74 ± 2.66	0.035	6.54 ± 1.80	0.021	0.044
VAS	8.31 ± 1.45	6.52 ± 1.72	0.011	3.34 ± 2.34	0.015	0.036

Abbreviations: FSFI, female sexual function index; ICPI, interstitial cystitis problem index; ICSI, interstitial cystitis symptom index; VAS, visual analog score.

[a]Group 1: study group.

[b]Group 2: control group.

TABLE 3 Change in domains of female sexual function index (FSFI) from baseline pretreatment period to postoperative period in the study group and in comparison to control group.

	Group 1[a] preoperative scores (n: 23), $X \pm SD$	Group 1[a] postoperative scores) (n: 23), $X \pm SD$	Preoperative and postoperative comparison of Group 1 (p value)	Group-2[b] scores (n: 23), $X \pm SD$	Preoperative scores of Group 1 versus Group 2	Postoperative scores of Group 1 versus Group 2
Desire	3.42 ± 0.59	4.97 ± 0.67	0.013	5.14 ± 1.02	0.014	0.442
Aurosal	3.91 ± 0.82	4.88 ± 1.67	0.021	5.23 ± 2.08	0.021	0.029
Lubrication	3.89 ± 0.54	4.43 ± 1.49	0.043	4.42 ± 1.84	0.456	0.856
Orgasm	3.19 ± 0.67	4.24 ± 1.62	0.035	5.02 ± 1.66	0.016	0.022
Pain	3.09 ± 0.98	4.84 ± 1.55	0.022	5.08 ± 1.96	0.018	0.132
Satisfaction	4.03 ± 0.58	4.98 ± 1.59	0.031	5.52 ± 1.84	0.035	0.046
Total	21.53 ± 7.02	28.34 ± 7.85	0.015	30.41 ± 8.32	0.029	0.234

Abbreviations: FSFI, Female sexual function index; ICSI, Interstitial cystitis symptom index; ICPI, Interstitial cystitis problem index; VAS, visual analog score.

[a]Group 1: study group.

[b]Group 2: control group.

urinary tract symptoms.[24] Bogart et al.[7] reported that 88% of women with IC/BPS were diagnosed with at least one or more pathological conditions associated with SD. More specifically, while 19% of women in the general population complained of arousal disorders, 61% of patients with IC/BPS indicated that they suffered from these disorders.[25] Statistically significant lower FSFI scores were shown in IC/BPS patients as compared to the control groups in the previous studies, and lower scores were highly correlated with the severity of symptoms.[26,27] Lower total FSFI score was shown in 47 IC/BPS patients compared to that of healthy women by Gardella et al. (16.8 ± 8.7 vs. 27.3 ± 6.4).[28] Similarly, Ottem et al.[26] reported lower scores at the pretreatment period in IC/BPS patients than in the control group (20.2 ± 9.6 vs. 29.9 ± 6.3). Here, it should be noted that the literature has established that a cut-off value of 26.55 indicates possible female SD.[29] When assessed above this threshold, we found that the scores in the study group were significantly lower than those in the control group in all domains of FSFI, except for lubrication during the pretreatment period.

The most common cause of SD in IC/BPS patients is dyspareunia, and its prevalence has been reported to range from 49% to 90%.[10,30] Sexual intercourse-induced pain in IC/BPS patients is considered a strong predictor of quality of life, and over half the percentage of IC/BPS patients were found to often avoid sexual intercourse with their partners.[31] Pinto et al.[32] have shown that BTX-A treatment significantly improved bladder pain and quality of life in patients with refractory IC/BPS. In our study, no objective questionnaire scoring system was used to assess the changes in quality of life after treatment. Despite that, patients reported in one-on-one interviews that improvements in sexual dysfunction increased their self-confidence and improved their overall quality of life. A study of 215 IC/BPS patients compared to 823 controls using the female sexual distress scale reported a rate of dyspareunia in women with IC/BPS (74.6%) versus the controls (29.9%).[27] The incidence of dyspareunia reported in our study was similar to that reported in the current literature.[7,8,24] Both the bladder and vaginal vestibule are derived from endoderm and genitourinary sinus tissue.[33] Dyspareunia may be due to direct compression of the bladder and/or irritation of the urethra during sexual intercourse. Even anticipation of dyspareunia during sexual activity can increase pelvic floor muscle tone, which aggravates the penetrative pain. Therefore, treatment of the urinary symptoms may lead to improvement in SD. Although the most commonly reported symptom in these women was pain during sexual activity, changes in libido, decreased lubrication, and orgasm frequency was also frequently reported compared with the rest of the population in the previous trials.[8–10]

TABLE 4 Changes in bladder diary components from the baseline pretreatment period to the postoperative period in the study group.

	Group 1[a] preoperative scores (n: 23), $X \pm SD$	Group 1 postoperative, scores) (n: 23), $X \pm SD$	Preoperative and postoperative comparison of Group 1 (p value)
Daytime frequency	13.6 ± 4.9	9.4 ± 3.5	0.009
Nighttime frequency	2.9 ± 1.5	1.9 ± 1.3	0.038
Mean voided volume (min–max) (mL)	126 (30–250)	159 (45–280)	0.024

[a]Group 1: study group.

Previous studies reported that conservative strategies, such as general relaxation, education, and behavior modification, are not efficacious in improving sexual function.[30] Further, studies investigating the improvement of SD in patients with IC/PBS following conventional treatments are very limited in the literature. Among studies on pharmacological treatments, Nickel et al. reported an improvement in sexual function following the use of PPS sodium. Meanwhile, several studies have investigated the effects of invasive treatments using various drugs, such as hyaluronic acid and chondroitin-sulfate, with conflicting results.[14,34] Specifically, Arslan et al.[14] reported a significant improvement in FSFI scores at the sixth month after intravesical instillation for both hyaluronic acid and chondroitin sulfate or only chondroitin sulfate as compared to those at the baseline pretreatment period. However, Kim et al.[34] and Liang et al.[35] reported neither improvement in symptoms nor significant changes in FSFI scores from baseline to the posttreatment period following the intravesical instillation of hyaluronic acid. Hung et al.[36] investigated the changes in sexual function of 87 sexually active women with IC/BPS after intravesical HA instillation and demonstrated statistically significant improvement in the total PISQ-9 score and three of the nine domain scores In this context, our study demonstrated that intravesical BTX-A treatment revealed a significant improvement in sexual function in women with IC/BPS. We showed a statistically significant improvement in the total FSFI score at the third month of the BTX-A injection. In addition, patients in the treatment group had statistically similar FSFI total scores and domain scores (e.g., desire, lubrication, and pain) to those in the control group. Although the mechanism of improvement in SD following oral and intravesical treatment with different agents has not been fully elucidated, regression of dyspareunia and improvement in urinary symptoms were considered the main reasons for this improvement.[13] BTX-A has been shown to reduce pain in spasticity, dystonia, and related conditions where pain reduction is the mainstay therapy.[37] BTX-A is thought to relieve pain through simple muscle relaxation, thereby reducing the compression of local blood vessels and inhibiting the release of neurotransmitters associated with pain and inflammation at the peripheral level.[38]

The ICSI and ICPI are widely used instruments to evaluate symptoms and treatment outcomes in patients with IC/BPS.[39] The present study also showed statistically significant changes in both indexes following the BTX-A injection. Similar to our results, the majority of trials reviewed in a recent meta-analysis documented significant changes in ICSI and ICPI scores following intravesical BTX-A injection.[40] Meanwhile, a mean reduction in VAS pain scores of 4.1 points following the injection of triangular BTX-A 100 U was reported in women with refractory IC/BPS.[41] We also observed a significant change in pain relief according to VAS scores. We observed a significant reduction in both daytime and nocturnal frequency at the end of the treatment period.

However, there are limitations to this study. First, it is a retrospective study that can be affected by all potential weaknesses stemming from its retrospective design. Second, the follow-up time was short, and the number of patients was relatively small. BTX-A has a limited duration of effect; therefore, the effect we observed in the study during the third month of BTX-A injection should be supported by the longer postoperative control period. Although significant amelioration was shown for all domains of FSFI in our study, 65.2% of patients in the study group were sexually active premenopausal women. Premenopausal women are predicted to have higher rates of improvement in sexual function compared to postmenopausal women after the intravesical injection of BTX-A. Prospective clinical studies with a larger series of patients and a higher proportion of postmenopausal patients are needed to characterize the nature of SD and to determine the improvement of sexual function in patients with IC/BPS after receiving intravesical BTX-A injection.

5 | CONCLUSION

Although bladder pain and lower urinary symptoms are prominent in the diagnosis of IC/BPS, the disease is associated with a remarkably high incidence of SD. Although several factors contribute to the pathogenesis of SD, pelvic and bladder pain appears to be the main factor contributing to the development of SD in IC/BPS patients. In addition to the improvement in pain and urinary symptoms, a significant beneficial effect on sexual function might be achieved following the intravesical injection of BTX-A. Patients can be informed of the potential benefits of BTX-A in improving sexual dysfunction.

AUTHOR CONTRIBUTIONS

Murat Topcuoglu: Project development, data collection, manuscript writing. **Murat Can Karaburun**: Data collection and data analysis. **Arif İbis**: Data analysis. **Mehmet İlker Gokce**: Data analysis. **Evren Süer**: Protocol/project development. **Omer Gülpınar**: Manuscript writing/editing/supervising.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Ankara Üniversitesi at https://www.ankara.edu.tr.

ETHICS STATEMENT

For this study, ethical approval was obtained from the local ethical committee (Ankara University Ethical Committee) (İ01-46-22). The consent statement form was obtained from all patients.

ORCID

Murat Can Karaburun http://orcid.org/0000-0001-6917-9051
Mehmet İlker Gokce http://orcid.org/0000-0002-2370-548X
Evren Süer http://orcid.org/0000-0003-4093-5436
Omer Gülpinar http://orcid.org/0000-0002-0869-708X

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