Injection location does not impact botulinum toxin A efficacy in interstitial cystitis/bladder pain syndrome patients

Robert J. Evans, MD,[1] Tyler Overholt, MD,[1] Marc Colaco, MD,[1]
Stephen J. Walker, PhD[1,2]

[1]Department of Urology/Female Pelvic Health, Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA
[2]Wake Forest Institute for Regenerative Medicine, Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA

EVANS RJ, OVERHOLT T, COLACO M, WALKER SJ. Injection location does not impact botulinum toxin A efficacy in IC/BPS patients. *Can J Urol* 2020; 27(1):10125-10129.

Introduction: *Botulinum toxin A (BTX-A) is currently used as a fourth-line therapeutic option for interstitial cystitis/bladder pain syndrome (IC/BPS) management. The purpose of this study was to determine if BTX-A injection can mitigate pain and if injection location (i.e. trigone-including versus trigone-sparing injection template) impacts treatment efficacy and/or treatment complications profile.*

Materials and methods: *Female IC/BPS patients refractory to conservative management strategies were prospectively enrolled and asked to complete a baseline history and physical exam, post-void residual (PVR) urine volume determination, O'Leary Sant (OLS) questionnaire, and Pelvic Pain and Urgency/Frequency Symptom Scale (PUF) questionnaire. Participants were randomly assigned to one of two treatment groups and received either: 1) a trigone-including BTX-A injection template or 2) a trigone-sparing injection template. Following therapy, patients were examined in clinic at 30 and 90 day post-treatment with symptom re-assessment via repeat questionnaires and for evidence of post-procedural complications.*

Results: *Compared to baseline, patients in both treatment groups experienced significant improvement in OLS and PUF scores at both 30 and 90 days post-treatment with BTX-A, regardless of which injection template was used ($p < 0.05$). Complications resulting from BTX-A were minimal (most commonly urinary tract infection (UTI) and urinary retention) and not significantly different between the treatment groups ($p > 0.05$). No distant spread of BTX-A was observed in any patient in either treatment group.*

Conclusions: *BTX-A treatment using either a trigone-sparing or trigone-including injection template resulted in significant, but not location-dependent, improvement in IC/BPS symptom scores at 30 and 90 day points post-procedure with no significant difference in post-treatment complication profiles.*

Key Words: interstitial cystitis/bladder pain syndrome, botulinum toxin A, trigone-sparing

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a heterogeneous, chronic disorder of unknown etiology that impacts millions of women and men in the United States.[1] Patients suffer from vague pelvic pain exacerbated by bladder filling and lower urinary tract symptoms such as frequency and urgency.[1] Since Alexander Skene's inception of the term "interstitial cystitis" in 1887, research into the pathophysiology underlying this disease has not successfully elucidated a specific mechanism and often reveals more questions than answers. As a result, diagnosis and management of patients with IC/BPS is difficult. Although there are a number of minimally invasive oral and intravesicular therapies available to treat IC/BPS, many patients remain refractory and require additional, more aggressive procedural therapies.

Botulinum toxin A (BTX-A) has long been considered an efficacious treatment for various pathologic bladder conditions such as overactive bladder (OAB) and neurogenic bladder, and the most recently published American Urological Association (AUA) guidelines have listed BTX-A as a fourth line treatment for IC/BPS (Grade C recommendation).[1] This guideline was based upon several observational studies and one randomized control trial that demonstrated variable amounts of short

Accepted for publication November 2019

Address correspondence to Dr. Stephen J. Walker, Wake Forest Institute for Regenerative Medicine, 391 Technology Way, Winston Salem, NC 27101 USA

and long term efficacy rates following BTX-A therapy for management of IC/BPS.[2-8] Further studies have additionally assessed the safety and efficacy of combining BTX-A injection with therapeutic hydrodistention, resulting in significantly increased symptom control without significantly increasing complication risk.[9-11]

While prior studies have demonstrated the efficacy of BTX-A as a therapy option for IC/BPS, they have not specifically addressed the importance of injection location on patient outcomes. The trigone of the bladder contains the majority of bladder nociceptors and is heavily innervated by both the parasympathetic and sympathetic nervous systems.[11-13] Given the anatomic considerations of bladder innervation, it stands to reason that BTX-A injections within the trigone should have a more significant effect on bladder pain than injections outside of the trigone. While trigonal injections have demonstrated a safe and effective method of treatment delivery,[14] the efficacy of trigonal injections has never been compared to trigone-sparing injection protocols. The purpose of this present study is to analyze the impact of injection location on the efficacy of BTX-A for management of IC/BPS patients. We hypothesize that an injection template that includes the trigone will be more efficacious at managing IC/BPS than a trigone-sparing template.

Materials and methods

Subjects

Approval was obtained from the Wake Forest University Health Sciences Institutional Review Board prior to the start of this study. Female patients ages 18-80 years old with a diagnosis of IC/BPS were prospectively enrolled. All patients included in the study were found to be refractory to conservative management strategies including oral pharmacological therapies, and were scheduled to receive BTX-A therapy. Patients with other urogenital or neurologic conditions were excluded from the study, including: any history of a urogenital cancer, urethral diverticulum, cyclophosphamide treatment, radiation treatment to the pelvis, bladder tuberculosis, active pregnancy, active herpes, spinal cord injury, stroke, Parkinson's disease, multiple sclerosis, or spina bifida. Informed consent was obtained from all patients prior to enrollment.

Intervention

Upon enrollment patients were randomly assigned to one of two intervention groups using a pseudorandom number algorithm and were blinded to their placement. One group of patients received BTX-A therapy using a trigone-sparing template and patients in the other group received BTX-A therapy using a trigone-including template, Figure 1. Botulinum toxin A was prepared by reconstituting 100 units BTX-A in 10 mL sterile saline to yield 10 units/mL. A total of 10 bladder injections (1 mL/injection) were delivered in a single BTX-A therapy session. All injections were given in the office setting using flexible cystoscopy and a local lidocaine instillation for anesthetic. With the exception of injection location, all other components of BTX-A therapy were identical between groups.

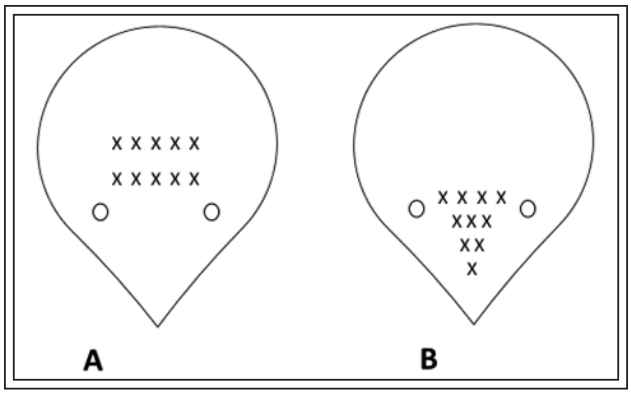

Figure 1. Botulinum toxin A injection templates used in this study: **(A)** trigone-sparing and, **(B)** trigone-including.

All patients completed a baseline history and physical exam, a post-void residual (PVR) urine volume determination, O'Leary Sant (OLS) questionnaire, and the Pelvic Pain and Urgency/Frequency Symptom Scale (PUF) questionnaire. Both the OLS and PUF questionnaires are well-validated in assessing IC/BPS pain and each comprised of two separate components: a symptom score and a problem score. Subjects returned to the clinic at 30 days and 90 days post-treatment for reassessment of IC/BPS symptoms using the OLS and PUF questionnaires and to address any complications that had occurred since the procedure. No subjects underwent repeat BTX-A therapy during this 90-day follow-up time period.

Statistical analysis

Two-tailed simple student t-tests were performed to compare continuous variable means including patient age, PVR result, OLS scores, and PUF scores. Chi-squared tests were performed for all categorical variable comparisons including presence of complications following BTX-A therapy. An analysis of variance (ANOVA) was performed to compare OLS and PUF scores at baseline, day 30, and day 90. Statistical significance was determined using a threshold p value < 0.05.

TABLE 1. **Patient demographics**

	Trigonal-sparing n = 14	Trigonal-including n = 12	p value
Age (years)	46.5 ± 12.6	50.2 ± 13.1	0.30
Race			0.79
White	13 (93%)	12 (100%)	
Non-White ethnicity	1 (7%)		
Gender			1
Female	14 (100%)	12 (100%)	

Results

A total of 27 female patients were prospectively enrolled in this study and one patient was lost to follow up. Table 1 shows descriptive statistics for the comparison of baseline patient demographic data. Demographic characteristics did not significantly differ between groups, indicating successful randomization of study groups, Table 1.

Clinical follow up and symptom reassessment

Table 2 displays baseline PVR and questionnaire data and follow up PVR and symptom reassessment data at 30 days and 90 days post-procedure.

PVR: There was no significant difference in follow up PVR between groups at 30 days ($p = 0.62$) or 90 days ($p = 0.50$; Table 2).

OLS questionnaire: ANOVA showed that both trigone-including and trigone-sparing groups had significantly higher OLS symptom and bother scores at baseline compared to scores at 30 and 90 day follow up visits (Figure 2, $p < 0.05$; Table 3). At the 30 and 90 day follow up visits, OLS-1 and OLS-2 scores were improved (i.e. lower) and not significantly different between trigone-including and trigone-sparing groups (Table 2, $p > 0.05$).

PUF questionnaire: Both trigone-including and trigone-sparing groups were also shown to have significantly

TABLE 2. **Pre- and post-treatment clinical characteristics**

	Baseline Mean (Std Dev)	p value	30 days Mean (Std Dev)	p value	90 days Mean (Std Dev)	p value
PVR		0.21		0.62		0.50
TI	29.17 (49.37)		30.6 (39.99)		41.1 (51.32)	
TS	14.36 (29.10)		40.9 (50.99)		59.33 (63.05)	
OLS symptom		0.42		0.38		0.21
TI	13.8 (17.41)		10.6 (3.17)		10.5 (3.75)	
TS	14.93 (3.03)		12 (3.77)		12.9 (4.23)	
OLS bother		0.78		0.36		0.74
TI	13.25 (3.26)		9.3 (4.27)		10.4 (3.31)	
TS	13.57 (2.61)		12.0 (3.83)		10.9 (3.38)	
PUF symptom		0.26		0.81		0.53
TI	14.25 (4.97)		13.1 (4.93)		12.7 (4.99)	
TS	16.57 (3.65)		13.6 (4.35)		14.0 (4.11)	
PUF bother		0.25		0.16		0.15
TI	8.25 (3.18)		6.4 (3.06)		6.5 (2.42)	
TS	9.07 (1.89)		8.2 (2.44)		8.1 (2.33)	

PVR = post-void residual; OLS = O'Leary Sant; PUF = Pelvic Pain and Urgency/Frequency Symptom Scale; TI = trigone-including; TS = trigone-sparing

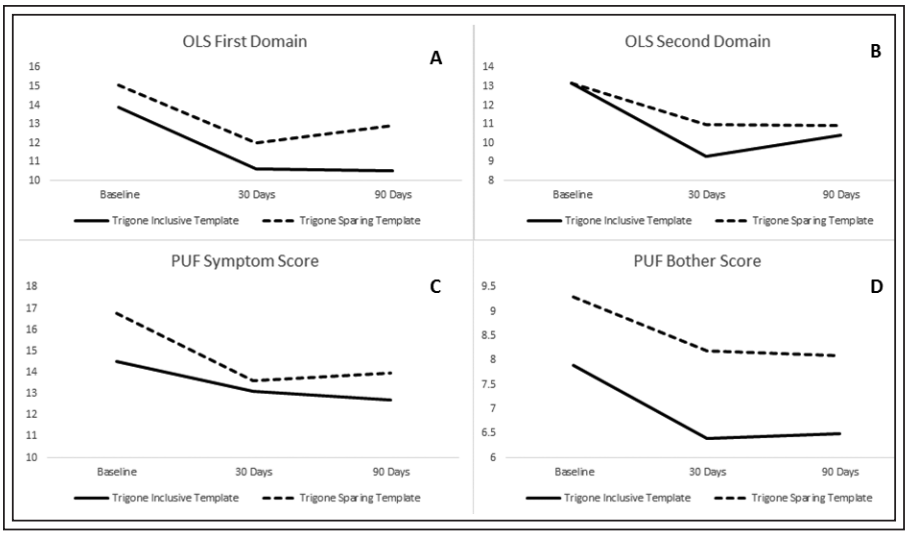

Figure 2. IC/BPS symptom score improvement for OLS and PUF questions at baseline, 30, and 90 days. **(A)** OLS symptom domain (ANOVA, p = .0053). **(B)** OLS bother domain (ANOVA, p = .0003). **(C)** PUF symptom score (ANOVA, p = .024). **(D)** PUF bother score (ANOVA, p = .031).

higher PUF symptom and bother scores at baseline compared to scores at day 30 day and 90 day follow up visits by ANOVA (Figure 2; $p < 0.05$). At 30 and 90 day follow up visits, PUF symptom and bother scores were improved (i.e. lower) and not significantly different between trigone-including and trigone-sparing groups (Table 2; $p > 0.05$).

TABLE 3. **ANOVA for questionnaire subgroups**

Questionnaire sub-group	F statistic	p value
OLS symptom	8.24	0.0053
OLS bother	14.24	0.0003
PUF symptom	5.32	0.024
PUF bother	4.81	0.031

OLS = O'Leary Sant; PUF = Pelvic Pain and Urgency/Frequency Symptom Scale

Complications: There was no significant difference between groups in the number of complications experienced following BTX-A therapy (Table 4; $p > 0.05$). The most common complications present in both groups following BTX-A therapy were urinary tract infection (UTI) and urinary retention. All cases of retention were managed with intermittent catheterization and were spontaneously resolved before conclusion of the study period. No vesicoureteral reflux or distant spread of botulinum toxin A was observed in any patient in either treatment group.

Discussion

This study builds upon the expanding body of literature that supports the use of BTX-A therapy for management of IC/BPS symptoms.[2-9] In spite of our original hypothesis that patients receiving BTX-A injection in the trigone would derive greater benefit than those getting the trigone-sparing injection template, we found that all of the participants in this study demonstrated significant symptomatic improvement, lasting for at least 90 days, regardless of the injection location. Both treatment groups experienced significant improvement when compared to baseline OLS and PUF scores for up to 90 days post-treatment, with no difference between groups in any of the four domains. We additionally found that there was no significant difference in complication rate between groups.

Avoidance of the trigonal region as a BTX-A injection site was thought to be due to a theoretical

TABLE 4. **Complications following BTX-A injection therapy**

Group	Complication rate	Complication event
Trigone-sparing (n = 14)	5/14	Urinary retention (2) Urinary tract infection (3)
Trigone-including (n = 12)	3/12	Urinary urgency (2) Urinary tract infection (1)

risk of vesicoureteral reflux with injection in this region compared to the posterior bladder wall[14] however none of our patients experienced this complication. These data agree with other published studies that have investigated trigone-including injection of BTX-A and suggest that not only are both injection locations equally efficacious, they are equally safe for patients.

Although we were able to populate the two treatment groups with randomly assigned patients that were effectively matched for age, ethnicity, baseline PVR, and baseline PUF and OSL symptom scores, a primary limitation of this study is the modest sample size and the lack of male participants. Moreover, the BTX-A injection procedures were performed at a single site, by a single urologist – study characteristics that may further limit the broader application of these results. While the outcomes reported here are both interesting and clinically relevant, the performance of additional studies that enroll larger number of patients, including male patients, across several clinical sites, could provide the necessary validation of the findings in this novel pilot study.

Conclusions

This study builds upon an expanding body of research on the management of IC/BPS. We found that there was no significant difference in the level of symptom improvement or in the number of complications in IC/BPS patients following botulinum toxin A treatment, regardless of whether a trigone-sparing or trigone-including injection template was used. Both injection templates were found to be equally effective for symptom improvement lasting for up to 3 months post-procedure. Urologists should thus be comfortable performing BTX-A injection therapy in IC/BPS patients using whichever injection template they feel most comfortable with. □

References

1. Hanno PM, Erickson D, Moldwin R, Faraday MM, American Urological Association. Diagnosis and treatment of interstitial cystitis/ bladder pain syndrome: AUA guideline amendment. *J Urol* 2015;193(5):1545-1553.
2. Smith JL. Case of the month. Interstitial cystitis. *J Am Acad Physician Assist* 2004;17(7):48.
3. Kuo HC. Preliminary results of suburothelial injection of botulinum a toxin in the treatment of chronic interstitial cystitis. *Urol Int* 2005;75(2):170-174.
4. 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 follow up. *J Urol* 2008;179(3): 1031-1034.
5. 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(4):704-709.
6. Ramsay AK, Small DR, Conn IG. Intravesical botulinum toxin type A in chronic interstitial cystitis: results of a pilot study. *J R Coll Surg* 2007;5(6):331-333.
7. Liu HT, Kuo HC. Intravesical botulinum toxin A injections plus hydrodistention can reduce nerve growth factor production and control bladder pain in interstitial cystitis. *Urology* 2007; 70(3):463-468.
8. 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(5):657-661.
9. Lorenzo L, Bonillo MA, Arlandis S et al. Hydrodistention plus Onabotulinumtoxin A in bladder pain syndrome refractory to conservative treatments. *Actas Urol Esp* 2016;40(5):303-308.
10. Lee CL, Kuo HC. Long-term efficacy and safety of repeated intravesical onabotulinum toxinA injections plus hydrodistention in the treatment of interstitial cystitis/bladder pain syndrome. *Toxins* 2015;7(10):4283-4293.
11. Pinto R, Lopes T, Silva J, Silva C, Dinis P, Cruz F. Persistent therapeutic effect of repeated injections of onabotulinum toxin a in refractory bladder pain syndrome/interstitial cystitis. *J Urol* 2013;189(2):548-553.
12. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. *Physiol Rev* 2004; 84(3):935-986.
13. Cruz F. Targets for botulinum toxin in the lower urinary tract. *Neurourol Urodyn* 2014;33(1):31-38.
14. Pinto R, Lopes T, Frias B et al. Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/ interstitial cystitis. *Eur Urol* 2010;58(3):360-365.