GYNECOLOGY

Bladder instillations vs onabotulinumtoxinA injection for interstitial cystitis/bladder pain syndrome: a randomized clinical trial

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BACKGROUND: Interstitial cystitis (IC)/bladder pain syndrome (BPS) is an unpleasant sensation related to the bladder with lower urinary tract symptoms lasting more than 6 weeks, unrelated to an otherwise identifiable cause. The etiology is likely multifactorial including urothelial abnormalities, neurogenic pain upregulation, and potentially bladder and vaginal microbiome alterations. Despite treatment effectiveness of both bladder instillations and intradetrusor onabotulinumtoxinA injection for this condition, a head-to-head comparison has not been performed.

OBJECTIVE: To compare the efficacy of bladder instillations and intradetrusor onabotulinumtoxinA injection for treatment of IC/BPS.

STUDY DESIGN: Patients with O'Leary-Sant (OLS) questionnaire scores of ≥6, meeting clinical criteria for IC/BPS, and desiring procedural management were randomized to bladder instillations or intradetrusor onabotulinumtoxinA injection. The primary outcome was the difference in OLS scores at 2 months posttreatment between groups. Secondary outcomes included evaluation of sexual function, physical/mental health status, pain, patient satisfaction, treatment perception, retreatment, and adverse event rates.

RESULTS: Forty-seven patients were analyzed with 22 randomized to bladder instillations and 25 to onabotulinumtoxinA injection. There were no differences in demographic and clinical characteristics between groups. From baseline to 2 months posttreatment, there was a decrease in OLS subscales in all patients (Interstitial Cystitis Symptom Index [ICSI] −6.3 (confidence interval [CI] −8.54, −3.95), $P<.0001$; Interstitial Cystitis Problem Index [ICPI] −5.9 (CI −8.18, −3.57), $P<.0001$). At 2 months posttreatment, patients in the onabotulinumtoxinA group had significantly lower OLS scores compared to those in the bladder instillation group (ICSI 6.3±4.5 [onabotulinumtoxinA] vs 9.6±4.2 [instillation], $P=.008$; ICPI 5.9±5.1 [onabotulinumtoxinA] vs 8.3±4.0 [instillation], $P=.048$). The difference in OLS scores between groups did not persist at 6 to 9 months posttreatment. There were no statistically significant differences between baseline and posttreatment time points for the remaining questionnaires. Eight percent of patients who received onabotulinumtoxinA injection experienced urinary retention requiring self-catheterization. Patients who underwent onabotulinumtoxinA injection were significantly less likely to receive retreatment within 6 to 9 months compared to patients who received bladder instillations (relative risk 13.6; 95% CI, 1.92−96.6; $P=.0002$). There were no differences between groups regarding patient satisfaction, perception of treatment convenience, or willingness to undergo retreatment.

CONCLUSION: Both onabotulinumtoxinA injection and bladder instillations are safe, effective treatments for patients with IC/BPS, with significant clinical improvement demonstrated at 2 months posttreatment. Our findings suggest that intradetrusor onabotulinumtoxinA injection is a more effective procedural treatment for this condition than bladder instillation therapy and associated with decreased rates of retreatment.

Key words: bladder instillation therapy, bladder pain syndrome, cystoscopy, interstitial cystitis, intradetrusor onabotulinumtoxinA injection, painful bladder syndrome, randomized controlled trial, clinical trial

Introduction

Interstitial cystitis (IC)/bladder pain syndrome (BPS) is an unpleasant sensation perceived to be related to the bladder that is associated with lower urinary tract symptoms, lasting more than 6 weeks and unrelated to infectious or otherwise identifiable cause.[1,2] Approximately 3 to 8 million U.S. women are affected,[3] with a predicted annual cost of $750 million in 2000.[4] There is a substantial psychological and general health impact, with increased rates of concurrent pain disorders, sleep and sexual dysfunction, and anxiety/depression.[5,6] The etiology is likely multifactorial to include structural defects, inflammatory, and functional alterations. The urothelium is normally coated with a glycosaminoglycan (GAG) layer,[7] and it is posited that GAG layer defects can contribute to IC/BPS by allowing penetration of irritants thereby affecting the underlying nerves and muscles. Neurogenic inflammation and pathologic C-fiber activation can result, which alters urothelial permeability, smooth muscle contractility, and blood flow.[8−10] Additionally, there may be bladder and vaginal microbiome alterations that contribute to IC/BPS.[11−13]

Both bladder instillation therapy (BIT) and intradetrusor onabotulinumtoxinA injection are effective in the treatment of IC/BPS.[8,10,14−23] Several components have been utilized for BIT, including GAG layer analogs, such as heparin, as well as anesthetic and anti-inflammatory agents. Given its effectiveness, widespread availability, and affordability, heparin combined with anesthetic has become one of the mainstay instillation cocktails.[14−18] Heparin replenishes GAG layer defects, enhances connective tissue healing, and inhibits inflammatory cell recruitment. Alkalinization of lidocaine with sodium

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AJOG at a Glance

Why was this study conducted?

Both bladder instillation and onabotulinumtoxinA injection therapy are effective for treatment of interstitial cystitis (IC)/bladder pain syndrome (BPS), but a direct treatment comparison is lacking.

Key findings

Intradetrusor onabotulinumtoxinA injection is more effective than bladder instillations for treatment of IC/BPS at 2 months posttreatment. This group difference was not seen at 6 to 9 months posttreatment. Patients who underwent intradetrusor onabotulinumtoxinA injection were 13.6 times less likely to receive any retreatment within 6 to 9 months compared to those who received bladder instillations. There was no difference in perceived convenience, satisfaction, or willingness to undergo retreatment between groups.

What does this add to what is known?

Intradetrusor onabotulinumtoxinA injection is safe, well tolerated, more effective, and associated with decreased rates of retreatment than bladder instillations for treatment of IC/BPS.

bicarbonate improves urothelial penetration, establishing more rapid peak concentrations of lidocaine and prevents precipitation when combined with heparin.[19] OnabotulinumtoxinA is a neurotoxin, which cleaves the snaptosomal-associated protein, preventing acetylcholine release into the neuromuscular junction and decreasing bladder contractility. It is hypothesized that onabotulinumtoxinA also reduces peripheral and central sensitization by decreasing nociceptive transmitter release and downregulating purinergic receptor expression, respectively.[20–23] The American Urological Association (AUA) recommends 100 units of intradetrusor botulinumtoxinA as an effective dose that minimizes urinary tract infection (UTI) and urinary retention.

The AUA's updated IC/BPS treatment algorithm modifies the previously tiered treatment structure. In patients with suspected Hunner lesion IC/BPS, operative cystoscopy is first line treatment. In patients with non-Hunner lesion IC/BPS, treatment options include behavioral/nonpharmacologic modifications, oral medications, bladder instillations, and procedural management.[2]

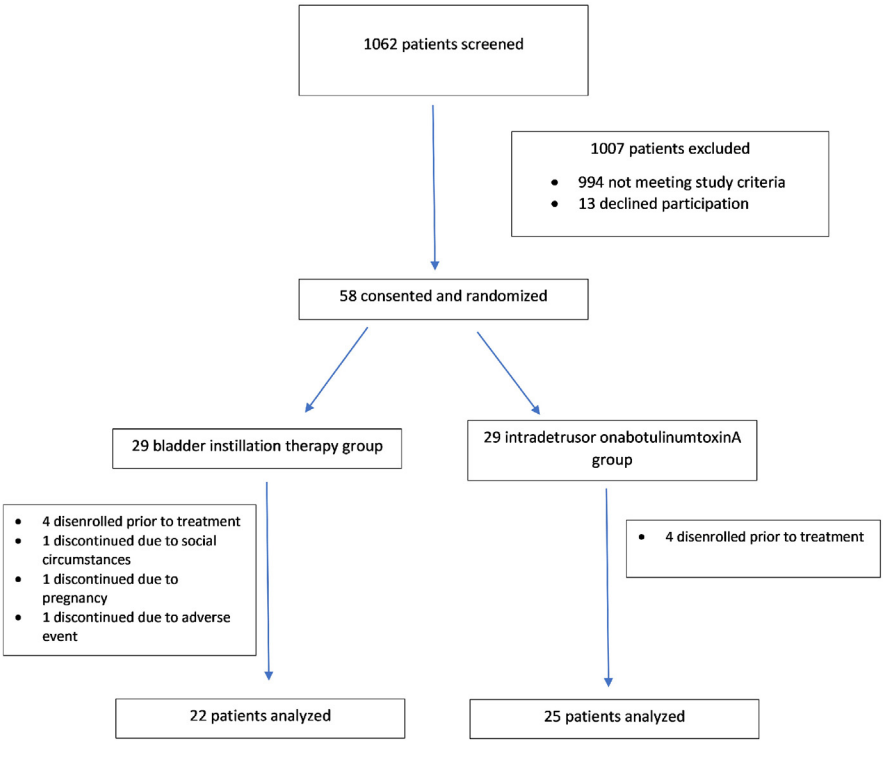
We compared the efficacy of BIT vs intradetrusor onabotulinumtoxinA injection therapy in treatment of IC/BPS. We hypothesized the intradetrusor onabotulinumtoxinA injection group would outperform the BIT group in O'Leary-Sant (OLS) questionnaire scores at 2 months posttreatment.

Materials and methods

This is a randomized trial from September 2020 to June 2023 performed at a single academic institution. This study received institutional review board approval and is registered at ClinicalTrials.gov. The Consolidated Standards of Reporting Trials guidelines are represented in Figure 1.

Female subjects 18 or older treated in the urogynecology clinic who met clinical suspicion for IC/BPS (urinary urgency, frequency, nocturia with pain component) and scored ≥6 on the OLS questionnaire were eligible for the study. The OLS is made up of the Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) and is widely utilized as a validated assessment of the severity and impact of IC/BPS symptoms, and a screening cutoff of 6 was utilized based on prior studies.[24,25] Exclusion criteria

FIGURE 1
CONSORT diagram



include patients who received BIT in the past 3 months or intradetrusor onabotulinumtoxinA injection in the past 6 months, postvoid residual (PVR) volume >200 mL, concurrent hydrodistension or sacral neuromodulation, untreated symptomatic prolapse ≥pelvic organ prolapse quantification stage 2, pregnancy, or inability to speak/read English.

Eligible patients interested in BIT or intradetrusor onabotulinumtoxinA injection therapy were consented and enrolled. Block randomization was performed using simple randomization with blocks of 6 in a 1:1 fashion. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes, which were individually opened after study enrollment to reveal the participant's randomized treatment group. Demographic data and validated questionnaires (OLS, Female Sexual Function Index [FSFI] [pain subset], Female Sexual Dysfunction Scale-Revised [FSDS-R], Short-Form 12 [SF-12] [which includes the Physical Component Score, Mental Component Score [MCS]], and visual analog scale [VAS]) were obtained at baseline by paper or electronic format.

Patients randomized to BIT were scheduled for 6 weekly instillations. Our institution's standardized bladder instillation consists of 40,000 international units heparin, 200 mg (mg) lidocaine, 2 mL 8.4% sodium bicarbonate, and sterile water for a 50 mL total volume. Our institution's BIT protocol involves cleansing the urethral meatus with povidone iodine or chlorhexidine, insertion of a lubricated 8 to 12-French catheter, bladder drainage, and then instillation of the bladder cocktail via gravity. The catheter was then removed and the patient advised to allow a minimum instillation dwell time of 30 minutes before spontaneous void. At each instillation visit, the participant was assessed for dysuria, urinary frequency/urgency, and/or hematuria suggestive of a UTI. If present, a catheterized urine sample was collected, and antibiotic treatment prescribed based on culture sensitivities. UTIs were defined as a positive culture with symptoms or patients who received empiric antibiotics for presumed UTI. Deviations in the instillation schedule of greater than 7 days from the scheduled visit were noted, and patients continued with therapy to complete a total of 6 instillations.

Patients randomized to the onabotulinumtoxinA group were scheduled for a 1-time procedure. If the preprocedural urinalysis demonstrated evidence of UTI, adequate antibiotic treatment was ensured prior to the procedure. Participants were offered a preprocedure anxiolytic (ie, 5−10 mg of oral diazepam) if desired. Ten mL of 2% lidocaine gel was applied into the bladder via the urethra and allowed to sit for 10 to 20 minutes before the start of the procedure. One-hundred units of onabotulinumtoxinA was reconstituted in 10 mL of preservative-free normal saline. Cystoscopy was performed and 0.5 mL reconstituted onabotulinumtoxinA was injected at a 3-mm depth, 1 cm apart along the posterior bladder wall for a total of 20 injections (4 rows of 5). Injections were performed by fellowship-trained urogynecologists, fellows, or obstetrics and gynecology residents with direct supervision. The patient received an antimicrobial prophylactically postprocedure.

Patients had 2 months posttreatment follow-up where they repeated the validated questionnaires. PVR volume was assessed in patients who reported incomplete bladder emptying symptoms, and patients with PVR volume above 200 mL were instructed on clean intermittent catheterization (CIC). If there was clinical suspicion for UTI, a urine specimen was collected and treatment based on positive culture. Patients had follow-up between 6 and 9 months where they completed the OLS questionnaire and nonvalidated study perception survey. Retreatment and adverse events were recorded via the electronic medical record. Patients could undergo retreatment 1 week after BIT or 3 months after intradetrusor onabotulinumtoxinA injection. Additionally, patients were allowed to cross over to the other treatment group if desired.

The primary outcome was treatment efficacy as measured by the OLS scores between groups at 2 months posttreatment. There is no established minimal clinically important difference (MCID) value for the OLS questionnaire. Prior literature suggests a mean change of 10 points corresponding to significant clinical improvement by alternative validated measures (ie, global response assessment, VAS).[26−28] We hypothesized the intradetrusor onabotulinumtoxinA injection group would outperform the bladder instillation group by a 30% difference in OLS scores, or estimated MCID of 10 points, at 2 months posttreatment. With an observed standard deviation in change of 3.5, the calculated effect size is d=3/3.5 (0.86), corresponding to a large effect size. With 80% power to detect a 10-point difference on the OLS with a 2-sided t test at an alpha=0.05, the calculated number of participants was 23 per group. Factoring in 20% dropout rate, a total of 58 patients, 29 per group, were needed for analysis. Secondary outcomes included evaluation of sexual function, general physical and mental health status, and pain scores at baseline and 2 months posttreatment as well as patient satisfaction, treatment perception, retreatment rates, and adverse events at 6 to 9 months posttreatment.

Baseline demographics were summarized using means and standard deviations and analyzed using t tests comparing the BIT and onabotulinumtoxinA treatment groups for continuous data. Categorical data were summarized using percentages and analyzed using chi-square test. OLS, FSFI, FSDS-R, SF-12, and VAS scores were analyzed using a 2-way repeated measures analysis of variance and summarized using means and standard deviations. Analyses were performed using JMP version 13.2 (SAS Corp, Cary, NC). Significance was set at 0.05 for all analyses.

Results

Fifty-eight patients were enrolled in the study, with 29 randomized to each group (Figure 1). Eight patients (4 in each group) disenrolled after randomization

but prior to treatment. Three patients randomized to the BIT group discontinued treatment, 1 due to social circumstances, 1 due to unplanned pregnancy, and 1 due to an adverse event. Analyses were performed on 47 patients (22 BIT group; 25 intradetrusor onabotulinumtoxinA injection group) with intention-to-treat analysis.

Baseline patient demographics in both groups were similar (Table 1). The majority of patients were premenopausal with an average body mass index of 28.7±5.9. Approximately one third of the study population was Black, one third was White, and 20% identified as Hispanic. Half of patients reported a history of chronic pain and psychiatric conditions including anxiety and/or depression with 20% of patients reporting a history of posttraumatic stress disorder with no significant differences between groups. Two thirds of patients had previous treatment for IC/BPS. During the trial, patients were continued on existing IC/BPS medications to simulate a more realistic approach, and there was no significant difference in concurrent medication use between groups. Baseline questionnaire scores were similar between groups with the exception of baseline MCS scores, where patients in the intradetrusor onabotulinumtoxinA injection group had higher scores, correlating to better mental health functioning (46.6±10.7 vs 38.1±14.1, P=.013).

From baseline to 2 months posttreatment, OLS scores decreased for all patients (ICSI −6.3 (CI −8.54, −3.95), P<.0001; ICPI −5.9 (CI −8.18, −3.57), P<.0001) (Table 2). At 2 months posttreatment, patients in the intradetrusor onabotulinumtoxinA injection group had lower OLS scores vs those in the BIT group, respectively (ICSI 6.3±4.5 vs 9.6±4.2, P=.008; ICPI 5.9±5.1 vs 8.3±4.0, P=.048) (Table 2 and Figure 2). Differences in OLS scores between groups were not maintained at 6 to 9 months. There were no statistically significant differences between baseline and posttreatment time points for the

TABLE 1
Demographic and clinical characteristics

Characteristics	Bladder instillation therapy (BIT) N=22	Intradetrusor onabotulinumtoxinA injection N=25
Age (y)		
18–25	1 (4.6%)	0 (0.0%)
26–35	5 (22.7%)	6 (24.0%)
36–45	5 (22.7%)	12 (48.0%)
46–55	6 (27.3%)	2 (8.0%)
56–65	4 (18.2%)	4 (16.0%)
>65	1 (4.6%)	1 (4.0%)
BMI (kg/m^2)	28.4±5.9	29.2±5.4
Race		
White	6 (27.3%)	9 (36.0%)
Black	8 (36.4%)	9 (36.0%)
Hispanic	4 (18.2%)	5 (20.0%)
Other	4 (18.2%)	2 (8.0%)
Premenopausal status	14 (63.6%)	17 (68.0%)
History of chronic pain	14 (63.6%)	10 (40.0%)
History of diabetes	1 (4.6%)	3 (12.0%)
Psychiatric comorbidities	15 (68.2%)	11 (44.0%)
History of PTSD	6 (27.3%)	4 (16.0%)
Current smoker	*3* (13.6%)	*2* (8.0%)
Previous treatment[a]	15 (68.2%)	16 (64.0%)
Concurrent BPS medications[b]	9 (40.9%)	6 (24.0%)
Concurrent PFPT	5 (22.7%)	5 (20.0%)
Baseline questionnaire scores		
OLS (0–36)		
ICSI (0–20)	13.2±3.7	11.8±3.9
ICPI (0–16)	11.8±3.3	10.9±3.2
FSFI (pain) (0–6)	1.9±2.0	2.7±2.0
FSDS-R (0–52)	25.0±18.0	17.3±17.3
SF-12 (0–100)		
PCS	42.3±10.0	41.2±9.7
MCS	38.1±14.1	46.6±10.7
VAS (0–10)	4.6±2.4	3.5±2.8

Data are mean±standard deviation, n (%) unless otherwise specified.

BMI, body mass index; *BPS*, bladder pain syndrome; *FSDS-R*, Female Sexual Dysfunction Scale-Revised; *FSFI*, Female Sexual Function Index, pain subset; *ICPI*, Interstitial Cystitis Problem Index; *ICSI*, Interstitial Cystitis Symptom Index; *MCS*, Mental Component Score; *OLS*, O'Leary-Sant; *PCS*, Physical Component Score; *PFPT*, pelvic floor physical therapy; *PTSD*, posttraumatic stress disorder; *SF-12*, Short-Form 12; *VAS*, visual analog scale.

[a] Previous treatments included dietary restrictions, pelvic floor physical therapy, medications, and procedures; [b] Concurrent medications included phenazopyridine, amitriptyline, hydroxyzine, anticholinergics, and beta-3-agonists.

TABLE 2
Two months posttreatment outcomes

Questionnaire scores	Bladder instillation therapy (BIT) N=22	Intradetrusor onabotulinumtoxinA injection N=25	*P* value	Grouped differences (2 mo−baseline) (95% CI)	*P* value
OLS (0−36)					
ICSI (0−20)	9.6±4.2	6.3±4.5	.008[a]	−6.3 (−8.55, −3.95)	<.0001[a]
ICPI (0−16)	8.3±4.0	5.9±5.1	.048[a]	−5.9 (−8.18, −3.57)	<.0001[a]
FSFI (pain) (0−6)	2.4±2.5	3.1±2.4	.711	1.0 (−0.169, 2.07)	.091
FSDS-R (0−52)	18.6±19.1	20.4±19.2	.654	−6.6 (−16.82, 3.57)	.186
SF-12 (0−100)					
PCS	45.1±11.2	43.4±11.1	.605	2.7 (−2.71, 8.15)	.303
MCS	41.7±10.5	47.6±8.8	.164	0.2 (−2.95, 3.25)	.920
VAS (0−10)	3.2±2.9	3.3±2.9	.975	−0.3 (−2.02, 1.39)	.701

Data are mean±standard deviation unless otherwise specified.

Group differences at 2-month time point were calculated via matched pairs analysis.

FSDS-R, Female Sexual Dysfunction Scale-Revised; *FSFI*, Female Sexual Function Index, pain subset; *ICPI*, Interstitial Cystitis Problem Index; *ICSI*, Interstitial Cystitis Symptom Index; *MCS*, Mental Component Score; *OLS*, O'Leary-Sant; *PCS*, Physical Component Score; *SF-12*, Short-Form 12; *VAS*, visual analog scale.

[a] Statistically significant.

remaining questionnaires (Figure 3). Perceived treatment convenience, patient satisfaction, and willingness for retreatment did not differ between groups with a mean follow-up time of 27 weeks (Figures 4 and 5). Three patients crossed over from their designated treatment group, all from BIT to intradetrusor onabotulinumtoxinA injection after a mean duration of 5 weeks after treatment. Per protocol analysis of the 6 to 9 month questionnaires did not show a difference between groups.

Twelve patients in the BIT group (55%) underwent retreatment within 6 to 9 months as compared to 1 patient in the intradetrusor onabotulinumtoxinA injection group (4%), with a risk reduction of 13.6 (CI 1.92 to 96.6, *P*=.0002). Six patients in both the intradetrusor onabotulinumtoxinA injection group and BIT groups experienced a UTI (*P*=.80). Two of 25 patients in the intradetrusor onabotulinumtoxinA injection group experienced urinary retention requiring CIC. One patient in the BIT group experienced self-limited side effects of metallic taste, dizziness, and nausea after her first 2 instillations; she declined to continue with BIT and proceeded with intradetrusor onabotulinumtoxinA injection.

Comment

Principal findings

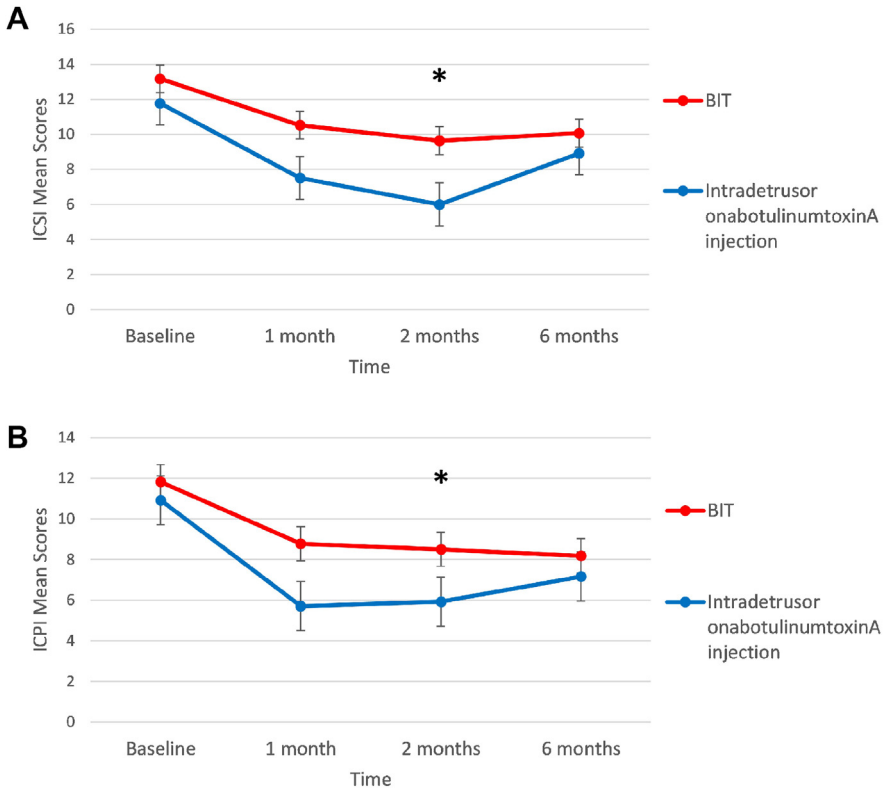
Patients undergoing BIT or intradetrusor onabotulinumtoxinA injection for treatment of IC/BPS experienced symptom improvement between baseline and 2 months posttreatment. Patients in the intradetrusor onabotulinumtoxinA injection group had significantly better OLS scores compared to BIT group at 2 months posttreatment. This difference was not maintained at 6 to 9 months posttreatment. There were no significant differences between groups in sexual function, physical and mental health status, and pain scores between baseline and 2 months posttreatment. Patients from both treatment groups had similar perceived treatment convenience, satisfaction rates, and willingness to undergo repeat treatment. Patients who underwent intradetrusor onabotulinumtoxinA injection were less likely to receive any retreatment within 6 to 9 months compared to those who received bladder instillations.

Results in the context of what is known

While neither are approved by the Food and Drug Administration for IC/BPS, the 2022 AUA IC/BPS treatment algorithm states that for non-Hunner lesion IC, either BIT or intradetrusor onabotulinumtoxinA injection therapy can be offered as initial treatment.[2] A variety of components have been utilized for BIT, including GAG layer analogs (heparin, hyaluronic acid, chondroitin sulfate), local anesthetics, and corticosteroids. There is growing evidence supporting serial, combined heparin and alkalinized lidocaine as an affordable and effective treatment for IC/BPS. Nomiya et al[17] utilized a similar instillation frequency and heparin and alkalinized lidocaine formulation as our study and reported an approximate 30% reduction between OLS scores at baseline and 1-month posttreatment. Cardenas-Trowers et al[18] evaluated the addition of triamcinolone acetonide to a heparin and alkalinized lidocaine-based instillation and reported no group differences after the 6-week instillation series, while reporting a 11% reduction in OLS scores between the first and sixth bladder instillations.

In a systematic review including 12 randomized controlled trials of intradetrusor onabotulinumtoxinA injection for patients with IC/BPS, there were significant improvements in OLS and VAS scores as well as daytime urinary

FIGURE 2
Longitudinal O'Leary-Sant (OLS) questionnaire scores



A graphical representation of the mean O'Leary-Sant subscale scores, (**A**) ICSI and (**B**) ICPI between patients who received BIT (red) and intradetrusor onabotulinumtoxinA injection (blue) across all time points (baseline, 1, 2 months, 6—9 months posttreatment). Longitudinal differences within groups were calculated using the repeated measures analysis of variance test. *Significance set at $P<.05$.
BIT, bladder instillation therapy; *ICPI*, Interstitial Cystitis Problem Index; *ICSI*, Interstitial Cystitis Symptom Index.

frequency, with a low incidence of serious adverse events in the onabotulinumtoxinA group.[29] Our study demonstrated greater symptomatic improvement in patients receiving onabotulinumtoxinA injection therapy compared to BIT therapy. We hypothesize this finding was due to the acute and neuromodulating effects of onabotulinumtoxinA, which may have a longer duration of effect compared to BIT.

While both BIT and intradetrusor onabotulinumtoxinA injection therapy have been shown to be effective for treatment of IC/BPS, a head-to-head comparison had not been performed. We demonstrated greater symptomatic improvement in patients who underwent intradetrusor onabotulinumtoxinA injection therapy at 2 months posttreatment.

Clinical implications

The updated AUA treatment algorithm equalizes nonsurgical management options for patients with non-Hunner lesion IC/BPS. However, clinical efficacy for oral pharmacologic treatments is limited, with studies demonstrating similar symptomatic relief between placebo and oral medications such as hydroxyzine, amitriptyline, and pentosan polysulfate.[30,31] Additionally, pentosan polysulfate, the only Food and Drug Administration-approved oral medication for treatment of IC/BPS, has been associated with potentially irreversible retinal pathology, thereby necessitating caution and regular ophthalmologic exams during treatment.[32] Given limited medical options as well as the average delay of 3 to 7 years from initial presentation to diagnosis of IC/BPS,[33,34] it is critical to consider procedural intervention earlier in the treatment course. Both BIT and intradetrusor onabotulinumtoxinA target the proposed underlying IC/BPS etiologies with demonstrated efficacy and low adverse event rates. It is important to counsel patients that while intradetrusor onabotulinumtoxinA injection is more invasive and carries a low risk of requiring CIC, its advantages include a single procedure compared to 6 to 8 weekly visits requiring catheterization.

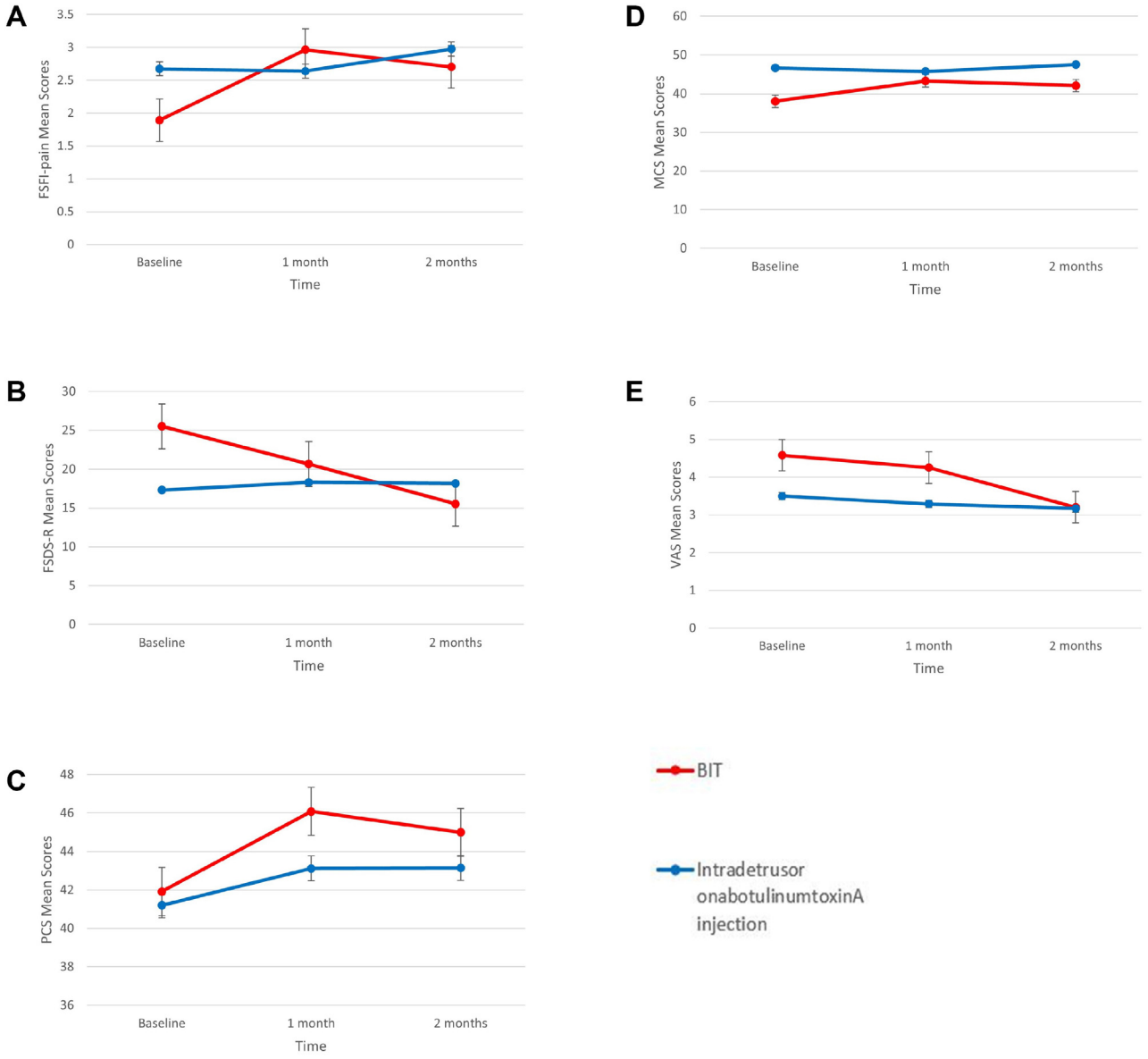
Our research also adds to the limited literature regarding the natural treatment time course with long-term follow-up so that clinicians can improve their counseling and manage patient expectations. As symptomatic differences between treatment groups were no longer apparent at 6 to 9 months posttreatment, repeat intradetrusor onabotulinumtoxinA injection therapy can be considered as often as every 3 months as needed to maintain symptomatic improvement. Additionally, more than half of the patients who underwent BIT underwent retreatment compared to only 1 patient who underwent intradetrusor onabotulinumtoxinA injection therapy. Patients should be counseled regarding this expectation as it may impact treatment preference, compliance, and patient satisfaction.

It is difficult to draw clear conclusions regarding the secondary outcomes from this data as we were not adequately powered. There were no statistically significant differences in secondary outcomes between baseline and posttreatment time points. Further investigation is necessary to evaluate impact of these treatments on physical, sexual, and mental well-being as IC/BPS can have a significant and understated impact.

Research implications

There is no established MCID for the OLS questionnaire in general or for comparing treatments at a single time point. Our study demonstrated differences between the treatment groups at the 2-month posttreatment time point, suggesting that the estimated OLS MCID of 10 points, or 30% difference, may be clinically applicable.

FIGURE 3
Baseline and post-treatment outcomes



A graphical representation of the mean baseline and posttreatment (**A**) FSFI, (**B**) FSDS-R, Short-Form 12 (comprised of (**C**) PCS and (**D**) MCS), and (**E**) VAS questionnaire scores between patients who received BIT (red) and intradetrusor onabotulinumtoxinA injection (blue). Longitudinal differences within groups were calculated using the repeated measures ANOVA test.

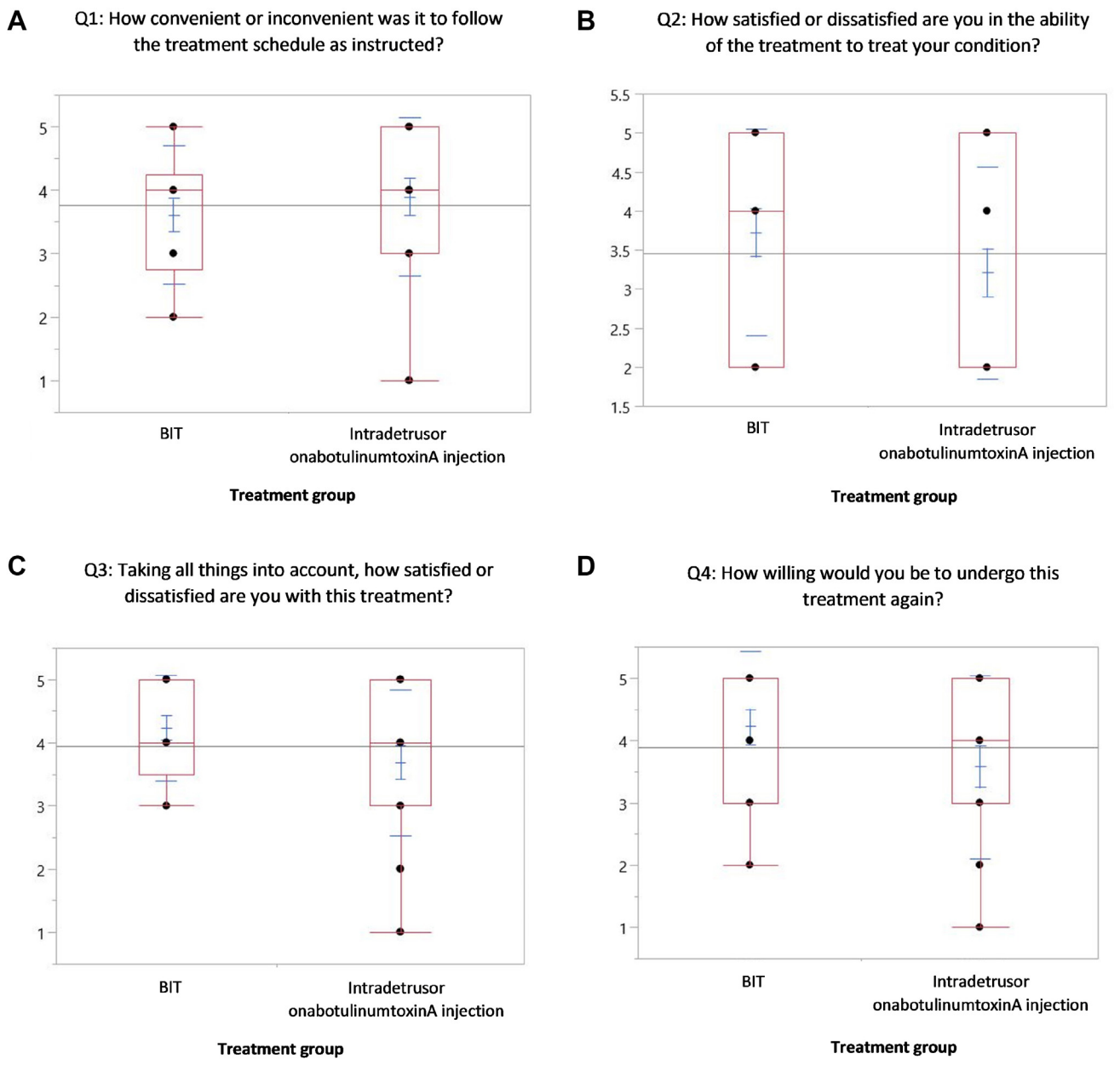
BIT, bladder instillation therapy; *FSDS-R*, Female Sexual Dysfunction Scale-Revised; *FSFI*, Female Sexual Function Index; *ICPI*, Interstitial Cystitis Problem Index; *ICSI*, Interstitial Cystitis Symptom Index; *MCS*, Mental Component Score; *PCS*, Physical Component Score; *VAS*, visual analog scale.

Additionally, our study population consisted of both patients who had received prior therapy as well as treatment-naïve patients. Further research to evaluate if prior treatment history impacts treatment response should be considered. A cost-effectiveness analysis between BIT and intradetrusor onabotulinumtoxinA injection is another potential topic of research, to evaluate cost of resource utilization, office visits, and time away from work. It is also important to note that our onabotulinumtoxinA injection pattern was trigone-sparing. As there is ongoing research investigating the benefit of trigonal injections for patients with IC/BPS, the optimal injection method remains unclear.

Strengths and limitations

A significant strength of this study is that it is the first to directly compare procedural treatment options for

FIGURE 4
Patient perceptions of treatment



Perceptions of (**A**) convenience, (**B & C**) satisfaction, and (**D**) willingness to repeat treatment were rated on a Likert scale of 1 to 5 (eg, extremely inconvenient, inconvenient, undecided, convenient, and extremely convenient). Differences between groups were calculated using a chi square test.
BIT, bladder instillation therapy.

IC/BPS. Additional strengths include its randomized design and standardized procedure of BIT and intradetrusor onabotulinumtoxinA injections. We utilized an evidence-based bladder instillation formulation, with commonly available and inexpensive components. Additionally, use of validated questionnaires, particularly the OLS to assess IC/BPS symptom improvement, improves our internal and external validity. Our patient population was diverse with patients of varying ages, races, and medical comorbidities increasing generalizability to other populations.

A limitation of our study is that we were underpowered for our primary outcome due to patient dropout in the bladder instillation group. Despite this, we are able to demonstrate significant differences between treatment groups at the primary time point. Another weakness is the difference in treatment

FIGURE 5
Nonvalidated 6 to 9 months post-treatment perception survey

Subject #_____

Post-treatment Perception Survey

	Extremely inconvenient	Inconvenient	Undecided	Convenient	Extremely convenient
How convenient or inconvenient was it to follow the treatment schedule as instructed?					
	Extremely dissatisfied	Dissatisfied	Undecided	Satisfied	Extremely satisfied
How satisfied or dissatisfied are you in the ability of the treatment to treat your condition?					
Taking all things into account, how satisfied or dissatisfied are you with this treatment?					
	Extremely unwilling	Unwilling	Undecided	Willing	Extremely willing
How willing would you be to undergo this treatment again?					

Non-validated 6 to 9-month post-treatment perception survey. Differences between groups were calculated using a chi square test.

modalities and the inability to blind the patients or researchers to the allocated treatment, which can introduce bias. Lastly, it is important to consider that IC/BPS may consist of different phenotypes, most notably with and without Hunner lesions, the former which may benefit from more bladder-centric therapy. While we did not differentiate between phenotypes, Hunner lesion IC/BPS comprises up to 7% of IC/BPS diagnoses,[35,36] patients could choose to crossover treatment groups, and we did not diagnose any Hunner lesion IC/BPS in study patients who underwent cystoscopy.

Conclusions

While both BIT and intradetrusor onabotulinumtoxinA injection are safe and effective for treatment of IC/BPS, patients receiving the latter demonstrated greater subjective improvement at the 2-month posttreatment time point with significantly reduced retreatment rates at 6 to 9 months posttreatment. Intradetrusor onabotulinumtoxinA injection may be a superior treatment modality for IC/BPS and should be discussed via shared decision

making between the clinician and patient. ■

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Clinical trial registration

i) Registration date: May 26, 2020.

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v) Data sharing information

a. Will individual participant data be available (including data dictionaries)? Yes.

b. What data in particular will be shared? Individual participant data that underlie the results

reported in this article, after deidentification (texts, tables, figures).

c. What other documents will be available? Study protocol.

d. When will data be available? Immediately following publication. No end date.

e. How will data be shared (including with whom, for what types of analyses, and by what mechanism)? Researchers who provide a methodologically sound proposal, to achieve aims in the approved proposal. Proposals should be directed to eva.k.welch.mil@health.mil. To gain access, data requestors will need to sign a data access agreement.

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