Transperineal Botulinum Toxin Injection for Chronic Pelvic Pain Syndrome after Transurethral Resection of the Prostate

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Purpose: To evaluate the efficacy of botulinum toxin type A (BTX-A) injection in patients with chronic pelvic pain syndrome (CPPS) after transurethral resection of the prostate (TURP).

Materials and Methods: Six patients after TURP received the injection of BTX-A around the prostate capsule or pelvic floor under ultrasound guidance. The clinical outcomes including overall pain intensity (assessed by visual analog scale, VAS), the Functional Pelvic Pain scale (FPPS), and mental state by anxiety and depression questionnaires, the generalized anxiety disorder (GAD-7) and Hamilton depression rating scale (HAM-D)) were assessed at pre-treatment, and 1, 4, 12 weeks after treatment.

Results: Six male patients, aged 65 to 76 years were enrolled. The improvement of VAS pain score, the Functional Pelvic Pain scale, and mental assessment were observed at 1, 4, and 12 weeks after treatment for all six patients. All 6 patients had no safety concerns through 12 weeks visit, except 3 patients complained of transient pain at the injection site.

Conclusion: Injection of BTX-A around the prostate under ultrasound guidance may be effective and safe for patients with CPPS after TURP.

Keywords: botulinum toxin type A; pelvic floor; pelvic pain; transurethral prostate resection; ultrasound

INTRODUCTION

Chronic pelvic pain syndrome (CPPS) is a significant pain condition with a major impact on quality of life. It is defined as a chronic or persistent pain perceived in structures related to the pelvis and is often associated with behavioral, sexual, and emotional consequences[(1)].

Common causes of CPPS in male patients include chronic prostatitis, chronic orchialgia, and prostatodynia. A cohort study including 51,529 male subjects indicated that 3.2% of subjects below 50 years old suffered from CPPS[(2)]. Transurethral resection of the prostate (TURP) has been widely used to treat benign prostatic hyperplasia and was considered to treat CPPS empirically in some clinical settings due to no reliable data[(3)]. However, whether the prostate surgery itself could cause CPPS is not well understood.

Currently, no specific therapies are available or suggested for TURP related CPPS. The empirical pharmacological treatments include non-steroidal anti-inflammatory drugs, α-receptor blockers, and muscle relaxants, in addition to pelvic floor physiotherapy. However, the efficacy of above treatments is doubtful and has never been confirmed in a large scale clinical trial.

Botulinum toxin, a potent neurotoxin extracted from Clostridium botulinum, can reversibly reduce excessive muscle tone by inhibiting the presynaptic release of acetylcholine[(4)]. It has been widely used to treat a variety of chronic pain disorders, such as migraine and refractory myofascial pain syndrome. Botulinum toxin has also been reported to improve symptoms of CPPS, including painful bladder syndrome, pelvic floor muscle spasms, and chronic prostatitis[(5-7)]. Two pilot randomized controlled studies observed a favorable effect towards pain relief with an injection of botulinum toxin type A (BTX-A) into the perineal skeletal muscle and prostate[(8,9)]. The European Association of Urology (EAU) Guidelines for Chronic Pelvic Pain (2020) recommended to use pelvic floor or prostate injections of BTX-A for the treatment of patients with primary prostate pain syndrome (level of evidence: 2B). Considering the heterogeneity in pathophysiological basis between primary PPS and CPPS (secondary to TURP), the effectiveness of BTX-A treatment for CPPS after TURP still needs more sufficient clinical data to demonstrate. In this study, we reported the clinical outcomes in 6 patients of CPPS after TURP receiving BTX-A injection.

MATERIALS & METHODS

Study population

The study was approved by the Yueyang Hospital academic committee and all participants gave informed

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Received December 2021 & Accepted June 2022

Table 1. Patient population and demographic data

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (year)	66	67	76	65	68	70
Previous surgery history	TURP	TURP	TURP	TURP	TURP	TURP
Pain duration (year)	1	1	2	1.5	1	2
Pain location	penis	anus	perineum	perineum	anus	perineum
Pain quality	stabbing pain	heavy pain	shooting pain	burning pain	heavy pain	shooting pain
Stool	constipation	constipation	constipation	constipation	constipation	constipation
Urinate	painful	painless	painful	painless	painless	painful
Transanal digital examination	Tenderness in the prostate area and the levator ani muscle	Tenderness in the prostate area	Tenderness in the prostate area	Tenderness in the prostate area	Tenderness in the prostate area and the levator ani muscle	Tenderness in the prostate area
Previous medications	gabapentin 600mg tid po venlafaxine 75mg bid po tramadol 100mg bid po	pregabalin 75mg bid po tramadol 100mg bid po	escitalopram 10mg bid po	pregabalin 75mg bid po	pregabalin 75mg bid po tramadol 100mg bid po	pregabalin 75mg bid po tramadol 100mg bid po
Previous interventions	pudendal nerve block	caudal epidural injection	none	none	pelvic floor electro-acupuncture	none

Abbreviations: TURP, transurethral resection of the prostate.

consent. Patients with CPPS after TURP from October 2019 to October 2020, in Pain Clinic, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai were enrolled. The diagnosis of CPPS was based on the EAU Guidelines for Chronic Pelvic Pain (2020), including 2 main criteria: 1) Pain in one or more locations of the pelvic area comprising penis, scrotum, perineum, suprapubic, anus, lasted for 3 months or above; and 2) Urological examinations (i.e., four glass urine tests) were normal. We excluded the patients with active urinary tract infection, genitourinary malignancy, history of neuromuscular disorder, or any contraindications to BTX-A treatment.

BTX-A injection under intrarectal ultrasound guidance

Prior to BTX-A treatment, we performed routine clinical evaluations, such as disease history, physical examination, laboratory tests (e.g., blood cell count, coagulation tests, urine analysis, urine culture and four-glass test), prostate ultrasonography, and pelvic MRI scan. The routine bowel preparation was required 1 day before, and the patients were requested to be fasted for at least 8 hours before BTX-A injection. Patients were placed in knee-chest position during the procedure. A biplane intrarectal ultrasound probe was used to display the residual prostate and urethra appropriately in the middle of the long axis. After sterile preparation of the perineal skin, a needle was placed near the prostate under ultrasound guidance (as shown in **Figure 1**), 0.5% lidocaine 10 mL was then injected around the residual prostate capsule. Patient with pelvic floor muscle tenderness received additional lidocaine injection (0.5% lidocaine 10 mL) in the hypertrophic muscle. When patients reported at least 50% improvement in their pain, measured by visual analog scale (VAS), after the diagnostic lidocaine injection received, BTX-A 100 IU (diluted to 10 IU/mL in 0.9% normal saline) injection was then performed around the prostate capsule and pelvic floor muscle on day 2 (**Figure1, 2**). The ultrasound

Table 2. Major outcomes before and after treatment at week 1, 4 ,12

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	mean ± SD
VAS							
Baseline	8	7	5	6	8	7	6.83 ± 1.17
Week1	6	5	3	4	5	4	4.50 ± 1.05
Week4	4	3	3	3	4	3	3.33 ± 0.52
Week12	4	3	3	4	4	4	3.67 ± 0.51
FPPS							
Baseline	14	12	11	11	15	14	12.83 ± 1.72
Week1	11	10	8	8	10	10	9.50 ± 1.22
Week4	8	7	6	6	7	7	6.80 ± 0.75
Week12	7	6	5	5	6	6	5.80 ± 0.75
GAD-7							
Baseline	12	11	9	8	12	11	10.50 ± 1.64
Week1	8	7	5	5	7	6	6.30 ± 1.21
Week4	6	5	5	4	5	6	5.17 ± 0.75
Week12	5	5	4	4	5	7	5.00 ± 1.09
HAM-D							
Baseline	35	26	21	22	32	30	27.67 ± 5.61
Week1	32	24	18	20	30	28	25.33 ± 5.61
Week4	25	18	16	18	24	22	20.5 ± 3.67
Week12	23	17	15	15	20	18	18.00 ± 3.10

Abbreviations: VAS, visual analog scale; FPPS, Functional Pelvic Pain scale; GAD-7, generalized anxiety disorder; HAM-D, Hamilton depression rating scale.

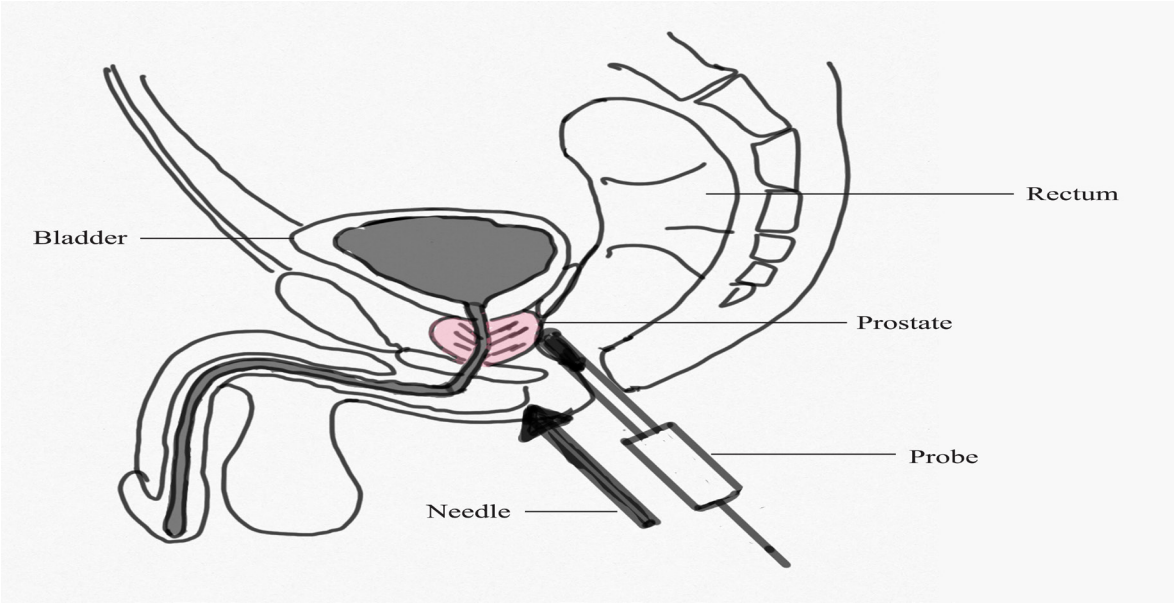

Figure 1. Schematic representation of entry point of the needle and position of the ultrasound probe

probe was placed in the rectum at 6 o'clock position, then rotated to 5 o' clock and 7 o'clock positions, respectively. The needle insertion point was 0.5 cm away from the midline of the perineum under intrarectal ultrasound guidance, then adjusted the direction of the needle to 5 injection sites around the prostate capsule (4 sites at the capsule of each lateral lobe, 1 site at the capsule of the posterior lobe), as shown in **Figure 3**. Each site received 20 IU injection. In addition, 2 patients received BTX-A injection to the levator ani muscle due to muscle tenderness. The total dose of BTX-A for each patient was 100 IU regardless of the injection sites.

Outcome measurement

Pain intensity, function, and mental status were assessed pre-treatment, and 1, 4, 12 weeks after treatment. Pain intensity was assessed by VAS. Overall function in relation to bladder, bowel, intercourse, walking, running, lifting, working, and sleeping were measured by Functional Pelvic Pain scale (FPPS). Mental state was evaluated with anxiety and depression questionnaire including generalized anxiety disorder (GAD-7) and Hamilton depression rating scale (HAM-D) (Supplement 1-3).

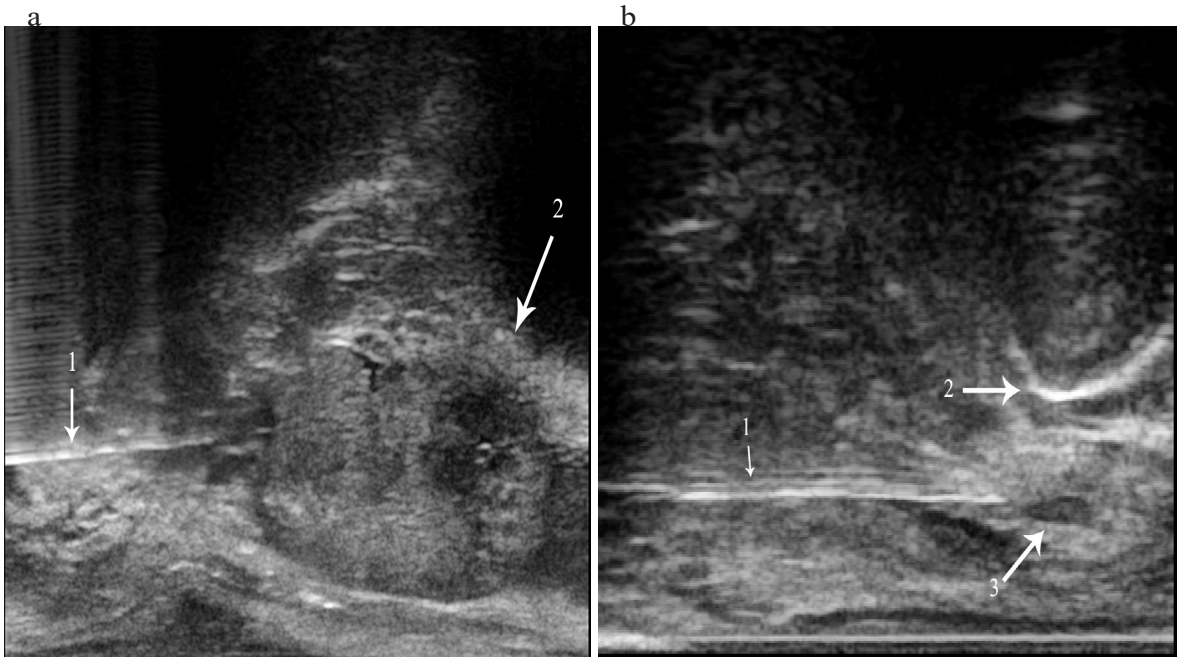

Figure 2. (a) Transrectal ultrasound guided BTX-A injection around the prostate. Arrow 1: needle; arrow 2: residual prostate; **(b)** Transrectal ultrasound guided pelvic floor muscle injection with BTX-A. Arrow 1: needle; arrow 2: ischiopubic ramus; arrow 3: levator ani muscle

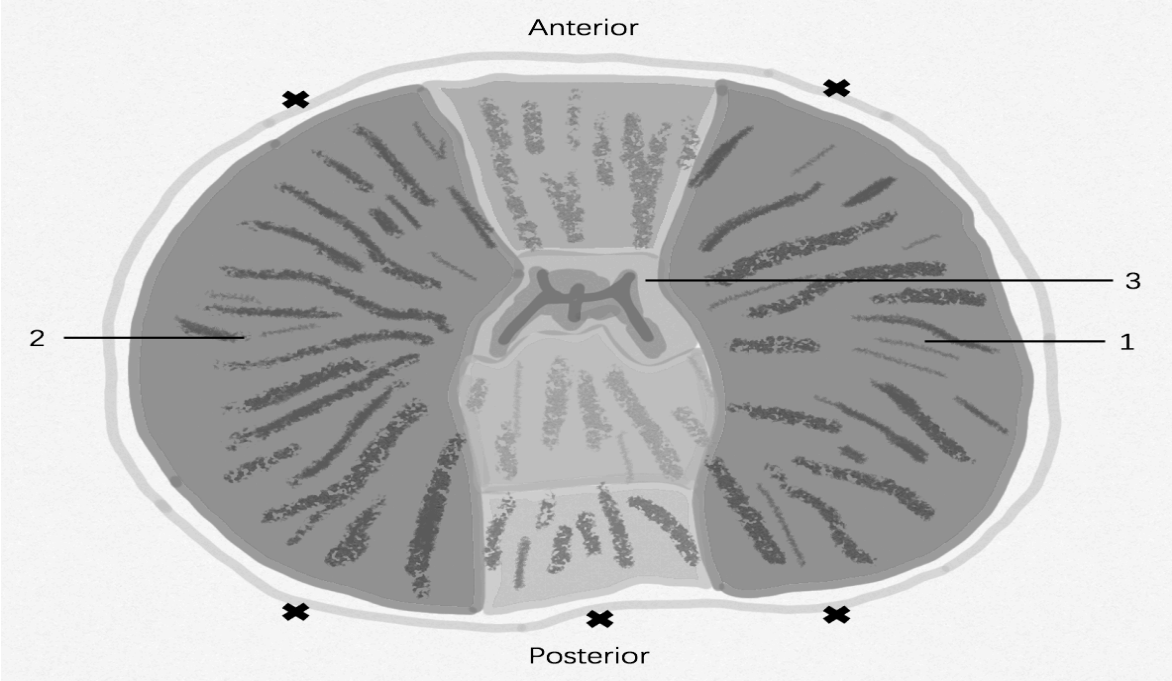

Figure 3. Schematic illustration of BTX-A injection site around the prostate capsule, shown in transverse section.
1 and 2: lateral lobe of the prostate; 3: urethra; The cross symbol represented the injection points.

Data collection

The clinical data including demography (e.g., age, BMI, duration of pain, onset of pain since TURP), diagnosis, baseline pain intensity, intervention (dosage regimen, injection site, etc.,) and clinical outcome measurements were collected (**Table 1, 2**).

RESULTS

Six male patients, aged 65 to 76 years, who met the CPPS diagnosis criteria were eligible to include in the BTX-A treatment. The average duration of CPPS was 15 months. All the patients had received transurethral prostatectomy for prostatic hyperplasia, and then developed chronic pelvic pain several months after the surgery. Digital anus examination showed tenderness in the prostate area for all the patients, and 2 of them had additional tenderness of the levator ani muscle. All the patients reported limited response to pharmacological therapies, complimentary treatment and/or nerve blocks.

Before BTX-A treatment, patients had a mean baseline VAS of 6.8. The mean VAS at week 1, 4 and 12 after the treatment was lower than the baseline. The mean FPPS also improved and decreased by around half at week 12 post-treatment. Psychometric assessment indicated all 6 patients had anxiety and depression before the BTX-A treatment. The mean score of GAD-7 and HAM-D decreased over time at follow-up visits.

There was no incontinence, urine retention, erectile dysfunction, muscle power loss over lower limbs or other severe adverse reactions during and after BTX-A treatment in all patients. 3 patients (50%) reported transient (less than 48 hours) pain in the injection site.

DISCUSSION

To our best knowledge, CPPS after TURP has not been reported in the literature. We demonstrated that BTX-A injection around the prostate capsule and/or the pelvic floor muscle might be an effective and safe therapy for CPPS after TURP.

Basically, CPPS might be the result of multiple factors, such as tissue adhesion from surgical scarring, local infection, pelvic floor dysfunction, and psychological conditions[1]. The etiology of CPPS after TURP is not fully understood. In our study, we did not find any exact causes for pain in all 6 patients according to MRI scan, ultrasound examination and urine test. Cystoscopy was conducted for three patients with consistent urinary pain symptoms, suggesting no obvious abnormal findings. All the patients did not experience any severe complications such as prostate capsule rupture in TURP. The possible explanation is adhesions forming from surgical scarring that could entrap nociceptive nerves, contributing to pelvic pain[10]. In addition, sensory receptors, pain mediators and nociceptive afferent neurons of the residual prostate also could play a role in developing the symptoms of pelvic pain after surgery[11].

Currently, there is no guidelines for the treatment of CPPS after TURP. The efficacy of non-steroidal anti-inflammatory drugs, anticonvulsants and other analgesics is still doubtful. BTX-A, an inhibitor of the chemical conduction process of neuron, is a promising treatment for several chronic pain conditions, such as migraine headache, temporomandibular disorder, focal dystonia, and refractory myofascial pain syndrome[12]. These promising results and good safety profile of BTX-A have triggered the interests using BTX-A to manage CPPS. Zermann et al. (2000) first reported transurethral urethral sphincter BTX-A injection for CPPS in 11 male patients. The pain score, peak urine flow, and residual urine volume were improved substantially after BTX-A injection[13]. A pilot double-blind and randomized placebo-controlled study of 30 patients with CPPS showed

that pain intensity score (VAS) decreased by 64.8, 75.6 and 80.0% at 1, 3 and 6 months after transurethral intraprostatic BTX-A injection compared with baseline, while no improvement of VAS observed in the placebo group (normal saline injection)[9]. In an uncontrolled clinical trial, 63 patients with refractory CPPS were divided into two groups according to different BTX-A injection routes. The results suggested that transrectal BTX-A injection had higher clinical improvement (defined as a reduction of 4 points or 25% in total chronic prostatitis symptoms index) compared to transurethral injection in patients with CPPS[14].

The mechanism of action for BTX-A in CPPS is unclear. BTX-A has been reported to inhibit the presynaptic release of acetylcholine and to reduce excessive muscle intensity[15]. In addition, animal studies have shown the anti-inflammatory effects of BTX-A by inhibiting the expression of cyclooxygenase-2 in prostate and spinal cord[16]. Since pain mediators and nociceptive afferent neurons of the prostate contributed to chronic pelvic pain, BTX-A was demonstrated to inhibit the release of excitatory neurotransmitter like glutamate from motor and sensory neurons, thereby diminishing central windup process and the development of central sensitization[17].

In this study, six patients developed CPPS after TURP surgery. Three of which had consistent urinary pain symptoms. We used transperineal BTX-A injection approach because the ultrasound-guided transperineal injection has a lower risk of complications (e.g., incontinence, urine retention, rectal injury and infection), compared with transrectal injection[8]. The results showed that the mean FPPS of 6 patients were reduced at week 12 after receiving BTX-A. The pain intensity was improved as well. The mean score of GAD-7 and HAM-D decreased over time, indicating the psychological component of CPPS was alleviated by BTX-A injection. In the future, we have to compare the transperineal and the transrectal route for injection of BTX-A for CPPS.

The reported adverse effects after BTX-A injection included constipation, stress urinary incontinence, fecal incontinence, and new stress urinary incontinence. The adverse effect seems to be dose-dependent, with a severe event (stress urinary incontinence) commonly observed in a dose higher than 300 IU[18]. We used 100 IU in our patient and there were no severe adverse effects observed in all six patient through 12 weeks except transient pain in the injection site for 3 patients.

CONCLUSIONS

BTX-A injection around the prostate and into the pelvic floor muscle under ultrasound guidance could be an option to provide significant pain relief and functional improvement in patients developed CPPS after TURP. Large scale clinical trial is warranted to verify the effectiveness and safety of ultrasound-guided transperineal injection of BTX-A in managing CPPS after TURP.

ACKNOWLEDGEMENT

This work was financed by Shanghai Committee of Science and Technology Project
(21Y11906100).

CONFLICT OF INTEREST

The authors report no conflict of interest.

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