Treatment of refractory category III nonbacterial chronic prostatitis/chronic pelvic pain syndrome with intraprostatic injection of onabotulinumtoxinA: a prospective controlled study

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Introduction: *To evaluate the efficacy and safety of intraprostatic injections of onabotulinumtoxinA (onaBoNT-A) to treat refractory chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).*

Materials and methods: *Prospective two-group controlled study. Treatment group included adult men with refractory category-III nonbacterial CP/CPPS who underwent transurethral intraprostatic injections of onaBoNT-A (200 U). Control group included comparable patients who underwent cystoscopy only. Primary outcome was the proportion of 6-point responders (≥ 6 points reduction of total score of National Institutes of Health-Chronic Prostatitis Symptom Index [NIH-CPSI]), at 3 months. Secondary outcomes included proportions of quality of life (QoL) responders (≤ 2 points in QoL domain), and global response assessment (GRA) responders (patients reporting moderately improved, or markedly improved), at 3 months. Other outcomes comprised changes from baseline NIH-CPSI scores, visual analog scale (VAS) sub-score of pain domain, PSA, prostate volume, post-void residual urine, and maximum flow rate. Significance was set at $p < 0.05$.*

Results: *Treatment group included 43 patients with mean age (SD) of 38.8 (7.3) years and mean duration of symptoms of 7.0 (2.9) years. At 3 months, the proportions of responders (NIH-CPSI 6-point, QoL, and GRA) were 72.1%, 69.8%, and 72.1%; which gradually declined to 37.2%, 25.7% and 27.9%, respectively, at 12 months. The baseline NIH-CPSI total score demonstrated -68.2% reduction at 3 months (-20.1 points; $p < 0.0001$); which gradually waned to -19% reduction (-5.6 points; $p < 0.0001$) at 12 months. Baseline VAS showed -79%, and -27.4% reductions at 3 and 12 months, respectively ($p < 0.0001$, each).*

None of control men has been 6-point, QoL nor GRA responder and none has demonstrated significant NIH-CPSI scores changes from baseline ($p > 0.05$, each). Compared to control, mean NIH-CPSI total scores of treated men at 1 and 3 months were significantly different ($p < 0.001$, each).

Conclusion: *OnaBoNT-A intraprostatic injections appeared to be effective and safe to ameliorate symptoms of refractory nonbacterial CP/CPPS; with pain most improved. The improvements gradually dwindled at 9-12 months.*

Key Words: chronic prostatitis/chronic pelvic pain syndrome, chronic prostatitis symptom index, onabotulinumtoxinA

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Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a highly prevalent disease that has been reported as the most commonly diagnosed urologic disease in young men < 50 years old, and the third most common urologic disease in men > 50 years old.[1] CP/CPPS dreadfully impacts patients' quality of life (QoL) with distressing morbidity comparable to status of angina pectoris, Crohn's disease, or following a heart attack.[2] Pain is the foremost complaint, which has been typically reported in the prostate, penis, perineum, testes, groin, pelvic floor, lower back, suprapubic area, and/or ejaculatory.[2,3] Unfortunately, treatment of category-III nonbacterial CP/CPPS[4] is one of the most challenging problems, with frequent frustrations for both patients and physicians. Several individual or combined therapies have been proposed; including antibiotics, anti-inflammatories, α-adrenergic receptor antagonists, and 5 α-reductase inhibitors.[5–8] Although these medications my benefit at least partially, many treatment-naive men, the evidence does not support such strategies for treatment-refractory patients. Additionally, adverse effects may outweigh the potential treatment effects, limiting patients' benefits.[5–8] Thus, a long list of second-line treatment approaches has been suggested for refractory patients with inconsistent outcomes.[8–12]

Although the mechanistic rationale for using onabotulinumtoxinA (onaBoNT-A) in the urinary tract is not well elucidated, onaBoNT-A injections have been successfully applied in several urologic conditions, including neurogenic and non-neurogenic detrusor overactivity, detrusor-sphincter dyssynergia, and interstitial cystitis/painful bladder syndrome.[13-15] Effects of onaBoNT-A on the prostate and benign prostatic hyperplasia have also been examined in several studies.[16–19] Although onaBoNT was reported to treat several other chronic pain syndromes,[20,21] less than handful of studies have documented using onaBoNT-A to treat CP/CPPS.[21–23]

The objective of our study was to examine the efficacy and adverse effects of intraprostatic injections of onaBoNT-A in treatment of refractory category-III nonbacterial CP/CPPS.

Materials and methods

Study design and setting

This prospective non-blinded two-group controlled study was conducted at our institution, from February 2011-May 2015. Ethics committee approved the study and each patient provided an informed consent.

Treatment group

Inclusion criteria: We enrolled adult men ≥ 20 years of age, with clinical category-III nonbacterial CP/CPPS, who were refractory to previous treatments. CP/CPPS was characterized according to the National Institutes of Health (NIH) as "prostate pain or pelvic pain with or without voiding symptoms for more than 3 months duration, in the absence of identifiable infection by standard microbiological methodology".[4] Patients were diagnosed using the constellation of symptoms of validated NIH-Chronic Prostatitis Symptom Index (NIH-CPSI),[4] prostatic tenderness, microbiologic findings of urine and/or expressed prostatic secretions, and exclusion of other diseases.

Exclusion criteria: Treatment-naive patients were not offered the option of onaBoNT-A injection. Patients with bacterial prostatitis, prostate cancer, urothelial cancer, urethral stricture, psychiatric disease or overt psychological behavior were excluded.

Baseline assessment: NIH-CPSI[4] was the instrument used to measure the CP/CPPS symptoms. NIH-CPSI is a validated self-assessment questionnaire that includes 3 domains (pain, urinary and QoL). It has a total score of 0-43 points, with higher scores indicate more symptoms. The extent of pain was evaluated using visual analog scale (VAS) sub-score of pain domain (0-10 points). Patients were also assessed for prostate-specific antigen (PSA), prostate volume (PV), post-void residual (PVR) urine volume, and maximum flow rate (Q-max). If a patient was taking any medication for CP/CPPS, he was required to withhold the medications a minimum of 2 weeks prior to baseline assessment.

Follow up: Treated patients were evaluated for NIH-CPSI changes and global response assessment (GRA) at 1, 3, 6, 9, and 12 month time points after injections. GRA questionnaire describes the overall symptoms changes compared to baseline in a seven-point scale ranging from -3 to +3 points (markedly worse to markedly improved, respectively).[24] PSA, PV, PVR, Q-max were re-tested at 1, 3 and 9 months after treatment. The treated men were required not to receive any other form of active treatment for CP/CPPS during the follow up. Patients violating the protocol were considered as withdrawals.

Outcome measurements: The primary outcome was the proportion of NIH-CPSI 6-point responders[24] (men reporting ≥ 6 points reduction of NIH-CPSI total score), at 3 months. Secondary outcomes included proportions of QoL responders (men reporting ≤ 2 points in QoL domain) and GRA responders (men reporting moderately improved, or markedly improved), at 3 months. Other measures comprised changes of NIH-CPSI total score, VAS sub-score, PSA, PV, PVR, and

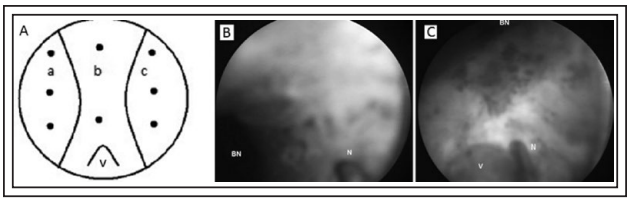

Figure 1. (A) Template of intraprostatic injections of onaBoNT-A. The injections were allocated uniformly and evenly throughout the prostate to minimize the areas of no effect; **(B)** Injection into the left lateral lobe, avoiding apparent blood vessels; **(C)** Injection into the urethral floor, proximal to verumontanum.
(a) right lateral lobe; **(b)** urethral floor; **(c)** left lateral lobe; v: verumontanum; BN: bladder neck; N: needle. • Indicates injection sites at lateral lobes and urethral floor.

Q-max; from baseline to follow up time points. Local and systemic adverse effects were reported.

Injections: A transurethral approach was utilized as a daycare setting, under general or regional anesthesia, with the patient in dorsal-lithotomy position. Each 100 U of onaBoNT-A (BOTOX, Allergan) were reconstituted in 4 mL of normal saline (25 U/mL). Eight intraprostatic injections (1 mL each; totaling 200 U) were deeply allocated; three in each lateral lobe and two in urethral floor proximal to verumontanum. The injection template is demonstrated in Figure 1. Care was given to avoid apparent blood vessels, and not to through-and-through puncture with the needle. At conclusion of the procedure, a urethral catheter was left indwelling, which was removed as soon as the patient was ambulating and having no significant hematuria.

Control group

Patients with similar inclusion/exclusion criteria who preferred cystoscopic examinations only as initial management were considered as control. They were evaluated at baseline and 1 and 3 months after cystoscopy in a similar fashion to the treatment group. Similarly, none of control men has received any form of active treatment for CP/CPPS during their 3 month follow up.

Statistical analysis: Data were analyzed using IBM-SPSS v22 software. Double-sided $p < 0.05$ was considered significant. Descriptive statistics were expressed as frequencies, proportions and/or mean with standard deviation (SD) and 95% confidence interval (95% CI). Differences at time points among paired continuous data were analyzed using general linear model-repeated measures ANOVA, while ordinary ANOVA was used to compare the treated group to control at different time points. Bonferroni adjustment for multiple comparisons was applied. Fisher's exact test was utilized to compare the dichotomous variables of treatment and control groups. Intention-to-treat (ITT) analyses were applied for the primary outcome (NIH-CPSI 6-point responders), and other treatment response dichotomous variables (QoL and GRA responders); by assuming worst-case scenario and considering all patients who withdrew as treatment

TABLE 1. **Treatment response in treatment group (intention-to-treat analysis, n = 43 men) and control group (n = 14 men)**

	1 month n (%)	3 months n (%)	6 months n (%)	9 months n (%)	12 months n (%)
6-point responders*					
Treatment	31/43 (72.1%)	31/43 (72.1%)	30/43 (69.8%)	24/43 (55.8%)	16/43 (37.2%)
Control	0/14 (0%)	0/14 (0%)	NA	NA	NA
QoL responders**					
Treatment	29/43 (67.4%)	30/43 (69.8%)	25/43 (64.1%)	14/43 (40.0%)	9/43 (25.7%)
Control	0/14 (0%)	0/14 (0%)	NA	NA	NA
GRA responders***					
Treatment	30/43 (69.8%)	31/43 (72.1%)	29/43 (67.4%)	23/43 (53.5%)	12/43 (27.9%)
Control	0/14 (0%)	0/14 (0%)	NA	NA	NA

Two-sided $p < 0.0001$, for all between treatment and control groups comparisons (Fisher's Exact Test)
*6-point responders = patients reporting ≥ 6 points reduction of NIH-CPSI total score
**QoL responders = patients reporting ≤ 2 points in QoL domain of NIH-CPSI
***GRA responders = patients reporting "moderately improved" or "markedly improved" in GRA
NIH-CPSI = National Institute of Health-Chronic Prostatitis Symptom Index; QoL = quality of life; GRA = global response assessment

failures and were included in the denominators. Per protocol analyses excluding withdrawing men were utilized for the continuous variables (NIH-CPSI scores, VAS sub-score, PSA, PV, PVR and Q-max).

Results

The treatment group included a total of 43 men with refractory CP/CPPS, mean age of 38.8 (7.3) years and mean duration of symptoms of 7.0 (2.9) years. The control group included additional 14 comparable patients with mean age of 36.7 (6.25) years and mean duration of symptoms of 8.1 (3.7) years ($p > 0.05$, each).

At 3 month follow up of treated men (intention-to-treat analyses of 43 patients), the proportions of NIH-CPSI 6-point, QoL, and GRA responders were 72.1%, 69.8%, and 72.1%, respectively. These favorable

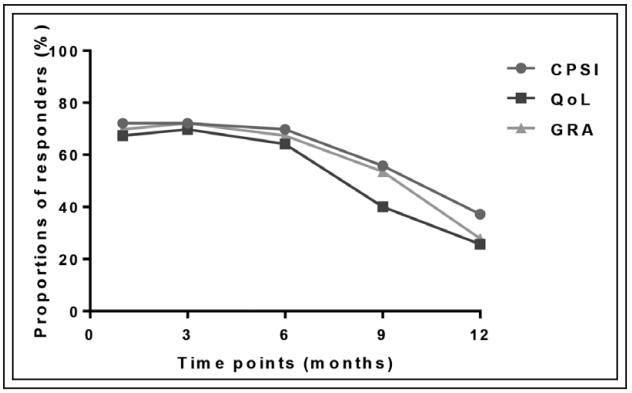

Figure 2. The proportions of treatment group responders at different time points (intention-to-treat analysis, n=43 men).

TABLE 2. **NIH-CPSI (total and domain) changes from the baseline of treatment group (per protocol analysis, n = 35 men)**

	Mean (SD)	Mean (SD) Mean difference (95% CI) % change				
	Baseline	**1 month**	**3 months**	**6 months**	**9 months**	**12 months**
NIH-CPSI (points)						
Total (0-43)	29.49 (5.07)	10.20 (6.81) -19.29 (-23.52, -15.05) -65.4%	9.37 (7.00) -20.11 (-24.61, -15.62) -68.2%	11.80 (6.24) -17.69 (-21.64, -13.74) -60%	19.88 (4.21) -9.61 (-11.88, -7.33) -32.6%	23.88 (4.84) -5.61 (-8.17, -3.05) -19%
Pain (0-21)	15.51 (3.08)	3.94 (4.14) -11.57 (-14.16, -8.98) -74.6%	3.14 (3.77) -12.37 (-14.91, -9.84) -79.8%	4.64 (3.23) -10.88 (-13.20, -8.56) -70.1%	10.99 (2.36) -4.52 (-5.95, -3.09) -29.1%	13.23 (2.91) -2.28 (-3.93, -.64) -14.7%
Urinary (0-10)	5.77 (2.14)	4.06 (1.21) -1.71 (-2.71, -.72) -29.6%	4.31 (1.73) -1.46 (-2.53, -.38) -25.3%	4.57 (1.81) -1.20 (-2.07, -.34) -20.8%	5.23 (1.48) -.54 (-1.52, .44)* -9.4%	5.89 (1.55) .12 (-.78, 1.01)* 2.1%
QoL (0-12)	8.20 (1.80)	2.29 (2.14) -5.91 (-7.48, -4.35) -72.1%	1.91 (1.915) -6.29 (-7.84, -4.73) -76.7%	2.58 (1.92) -5.62 (-7.12, -4.12) -68.5%	3.69 (1.88) -4.51 (-5.76, -3.25) -55%	4.96 (2.22) -3.24 (-4.66, -1.82) -39.5%
VAS (0-10)	7.63 (1.59)	1.97 (1.99) -5.66 (-6.97, -4.34) -74.2%	1.60 (1.52) -6.03 (-7.20, -4.85) -79%	2.10 (1.59) -5.53 (-6.72, -4.34) -72.5%	3.78 (1.23) 3.85 (-4.73, -2.97) -50.5%	5.54 (1.57) -2.09 (-2.98, -.1.12) -27.4%

%represents the percentage change from the baseline mean
$p < .01$ for all NIH-CPSI comparisons to baseline (*except urinary domain at 9 and 12months [$p > .05$, each]
$p < .0001$ for each VAS comparison to baseline
NIH-CPSI = National Institute of Health-Chronic Prostatitis Symptom Index; QoL = quality of life; VAS = visual analogue scale; 95% CI = 95% confidence interval

TABLE 3. **Comparisons of NIH-CPSI total scores of treatment group (per protocol analysis; n = 35 men) and control group n = 14 men)**

	Treatment	Control	p value
Mean NIH-CPSI total score (points)			
Baseline	29.49 (5.07)	27.1 (4.8)	> 0.05
1 month	10.20 (6.81)	26.1 (5.5)	< 0.001
3 months	9.37 (7.00)	27.0 (6.0)	< 0.001

NIH-CPSI = National Institute of Health-Chronic Prostatitis Symptom IndexC

treatment responses have continued through the 6 month follow up, then the proportions of responders have gradually declined over time to reach 37.2%, 25.7% and 27.9%, respectively, at 12 months, Table 1 and Figure 2. On the contrary, none of the control men has demonstrated 6-point, QoL nor GRA response at the 1 and 3 month follow up, Table 1.

The NIH-CPSI total and domain scores and VAS sub-score changes from baseline of treated men are shown in Table 2. Thirty-five men were included in per protocol analyses of these continuous variables after excluding eight men who withdrew. At 1 month, NIH-CPSI total score was significantly reduced to 10.2 (6.8), with a mean difference of -19.29 points (-65.4%, $p < 0.0001$). The significant favorable treatment effects were persistent during 3 and 6 month follow up, with NIH-CPSI mean differences of -20.1 and -17.7 points (-68.2% and -60%), respectively, ($p < 0.0001$, each). NIH-CPSI mean differences gradually waned to -9.6 and -5.6 points (-32.6% and -19%) at 9 and 12 months, respectively. Yet, all NIH-CPSI total and domain changes at all time points were significant compared to baseline ($p < 0.01$); except the urinary domain at 9 and 12 months ($p > 0.05$, each). VAS sub-scores of pain domain demonstrated highly significant improvements ($p < 0.0001$, each) at all time points compared to baseline; with as high as -79%, and as low as -27.4% improvements at 3 and 12 months, respectively. On the other hand, none of control patients has demonstrated significant NIH-CPSI scores changes from baseline ($p > 0.05$, each), at 1 or 3 months after cystoscopy. Compared to mean NIH-CPSI total scores of control men at 1 and 3 months (26.1 ± 5.5 and 27.0 ± 6.0 points, respectively), the NIH-CPSI scores of treated men were significantly different ($p < 0.001$, each) as shown in Table 3.

TABLE 4. **Changes of PSA, PV, PVR and Q-max from the baseline of treatment group (per protocol analysis, n = 35 men)**

	Mean (SD)	Mean (SD) Mean difference (95% CI) % change		
	Baseline	**1 month**	**3 months**	**9 months**
PSA (ng/mL)	1.05 (.54)	1.22 (.56) .17 (.07, .26) 16.2% p < .0001	.87 (.44) -.18 (-.31, -.05) -17.1% p < .002	.91 (.55) -.14 (-.27, -.01) -13.3% p < .03
PV (mL)	28.83 (10.43)	31.16 (11.23) 2.33 (1.50, 3.17) 8.1% p < .0001	25.19 (8.67) -3.64 (-4.95, -2.33) -12.6% p < .0001	24.21(9.31) -4.62 (-5.91, -3.33) -16% p < .0001
PVR (mL)	48.03 (36.25)	33.05 (23.75) -14.98 (-27.58, -2.37) -31.2% p < .013	28.77 (19.65) -19.25 (-32.22, -6.29) -40.1% p < .001	31.64 (22.51) -16.39 (-29.02, -3.76) -34.1% p < .005
Q-max (mL/sec)	16.11 (5.63)	19.83 (5.41) 3.71 (2.93, 4.50) 23% p < .0001	22.28 (7.19) 6.16 (4.69, 7.63) 38.2% p < .0001	19.34 (5.96) 3.23 (1.51, 4.95) 20% p <.0001

%represents the percentage change from the baseline mean
PSA = prostate specific antigen; PV = prostate volume; PVR = post void residual urine volume; Q-max = maximum flow rate

Of treated men, all changes of PSA, PV, PVR and Q-max from baseline were significant at all time points ($p < 0.05$, each), Table 4. PSA was initially raised by 16.2% ($p < 0.0001$) at 1 month, followed by -17.1% ($p < 0.002$) and -13.3% ($p < 0.03$) reductions from baseline at 3 and 9 months, respectively. Similarly, PV demonstrated initial increase (8.1%) at 1 month, followed by -12.6% and -16% reductions from baseline at 3 and 9 months, respectively, ($p < 0.0001$, each). Significant PVR reductions (-31.2%, -40.1% and -34.1%; $p < 0.01$, each), and Q-max improvements (23%, 38.2% and 20%; $p < 0.0001$, each) were demonstrated at 1, 3, and 9 months, respectively, compared to baseline, Table 4.

None of the treated patients has demonstrated serious local or systemic side effects after the procedure. Non-significant gross hematuria was noted in 29 (67.4%) men, which has resolved spontaneously within 2-7 days. Dysuria was reported in 31 (72.1%) patients, which has also resolved spontaneously within 3-10 days. No patient reported stress urinary incontinence, ejaculatory disorders, altered erectile functions, urinary tract infections, fever, or sepsis.

Discussion

The pathophysiology of CP/CPPS is uncertain with several mechanisms have been proposed, among them is abnormal prostate sensory functions.[25–29] The prostate contains abundant nociceptive and non-nociceptive afferent neurons, and sensory C-fibers which may contribute to pain or irritative voiding symptoms of CP/CPPS.[25-27] Additionally, acetylcholine and muscarinic receptors have been reported to stimulate prostate glandular secretions and growth.[25,28] On the other hand, noradrenaline has been reported to induce α1-adrenergic activation and prolonged bladder and prostate smooth muscle contractions, to further aggravate the symptoms.[29]

The mechanism of action of onaBoNT-A was previously thought to be mediated only via prolonged blocking of presynaptic release of acetylcholine at neuromuscular junctions.[20] Recent data, however, support the belief that onaBoNT-A acts also on sensory pathways.[20,25–29] Furthermore, the anticholinergic effects of onaBoNT-A were reported to extend into the neuroglandular junctions decreasing glandular secretions.[30,31] Moreover, injecting onaBoNT-A into rat prostates has been reported to down-regulate α 1A-adrenergic receptors, inhibit proliferation, induce apoptosis, and result in tissue atrophy.[32]

Few previous reports have suggested that onaBoNT may represent a useful modality to treat nonbacterial CP.[21–23] Zermann et al[22] reported on transurethral injection of onaBoNT-A into external sphincter of CP men, noting significant improvements. Conversely, Gottsch et al[23] injected onaBoNT-A into perineal muscles of CP men; reporting only modest improvements in GRA and non-significant changes of NIH-CPSI at 1 month.

In the current research, we studied challenging cohort of adult patients with longstanding refractory category-III nonbacterial CP/CPPS. None of our patients was treatment-naive, and all had received multiple earlier treatments and experienced several treatment failures. NIH-CPSI 6-point score reduction was adopted as the primary outcome measure; which has previously been shown to be the optimal threshold to predict response, with 77% sensitivity and 71% specificity.[24] QoL domain, and GRA at 3 months were both utilized as additional tools to measure the treatment response. GRA evaluates the perception of changes in symptoms, which has been previously reported to correspond to changes in NIH-CPSI scores.[24]

The clinically and statistically significant favorable treatment responses to onaBoNT-A intraprostatic injections were apparent in our study. Of treatment group, at 3 months, 72.1% were NIH-CPSI 6-point responders, 69.8% were QoL responders, while 72.1% were classified as GRA responders. The favorable treatment responses were persistent through 6 month follow up, as 69.8% of men were NIH-CPSI 6-point responders. Although the favorable effects dwindled gradually in many patients over the succeeding months, at 9 and 12 months, the proportions of NIH-CPSI 6-point responders were still as high as 55.8% and 37.2%, respectively.

The favorable treatment effects were prompt, since treatment responders have experienced obvious improvements as early as 1 month, with statistically highly significant and clinically meaningful total NIH-CPSI mean difference of -19.29 points (-65.4%; $p < 0.0001$), compared to baseline. Significant treatment effects were persistent during 3 and 6 month follow ups, with total NIH-CPSI mean differences of -20.11 (-68.2%; $p < 0.0001$) and -17.69 (-60%; $p < 0.0001$) points, respectively. Total NIH-CPSI mean reductions then gradually faded to -32.6% and -19% at 9 and 12 months, respectively. Yet, NIH-CPSI total score changes at all follow up time points were highly significant compared to baseline ($p < 0.0001$) and of clinical relevance since all differences were markedly > 0.5 SD of the baseline measurement. Half a SD of the first measurement has been reported as a minimal change to discriminate the clinical relevance of outcomes of treatment of chronic diseases.[33]

Although all NIH-CPSI domains of treated men, except urinary domain at 9 and 12 months, have demonstrated significant improvements, it is the

pain domain and VAS sub-score changes that have driven these improvements. Pain domain score has demonstrated highest improvement ($p < 0.0001$) at 3 months with -79.8% reduction of baseline mean. Pain domain continued the improvement at 6 months (-70.1%); then started to wane to -29.1% and -14.7% at 9 and 12 months, respectively. Similarly, VAS sub-score improvement ($p < 0.0001$) at 3 months (-79%) has continued at 6 months (-72.5%); then gradually waned to -50.5% and -27.4% at 9 and 12 months, respectively. Again, all pain and VAS changes at all time points were statistically significant and clinically relevant. The significant changes of PSA, PV, PVR and Q-max after injections compared to baseline further exhibit the beneficial effects of the treatment.

To minimize the potential placebo effects of treatment, we included a control group of comparable men who preferred to have cystoscopic examinations only as initial management. In contrast to the favorable outcomes of treatment, none of control men has demonstrated 6-point, QoL or GRA response. Additionally, all control men have reported non-significant NIH-CPSI scores changes at 1 and 3 months after cystoscopy ($p > 0.05$, each). The significant differences ($p < 0.001$, each) between mean NIH-CPSI scores of treated and control men at 1 and 3 months further jeopardize the possibility of placebo effects of treatment. Furthermore, patients with chronic pain conditions, as is the case of our patients, often attempt many unsuccessful therapies, which could in turn generate negative expectations for new treatments.[7]

The procedures of injections were associated with no serious local or systemic adverse effects. Transient exaggeration or "flare" of dysuria was the most noticeable complaint reported by our patients (72.1%) after the procedure.

Limitations and strength

Our controlled study was neither randomized nor blinded, with its inherent drawbacks. Consequently, the evidence provided from our study is low, compared to that of the more rigorous randomized controlled trials (RCTs). Large-scale blinded RCTs should minimize the bias, decrease the placebo effect, determine the actual treatment effect size more precisely and provide a higher level of evidence. However, in an effort to overcome these limitations, we have used several other handy research tools. We have included a comparable group of men with similar inclusion/exclusion criteria as a control. Additionally, we have adopted NIH-CPSI 6-point reduction (rather than the frequently used 4-point reduction) as a primary outcome,[24] used GRA, applied ITT analyses of the primary outcome and other treatment response dichotomous variables (considering all withdrawals as treatment failures), and utilized "half a SD of baseline measurements" as a tool to assess the clinical relevance of our outcomes.

Conclusion

In conclusion, our initial findings suggest that intraprostatic injections of onaBoNT-A might be effective and safe to ameliorate symptoms of refractory category-III nonbacterial CP/CPPS. Pain was most improved. The beneficial responses continued at 6 months, then gradually waned at 9-12 months. Considering the limitations of this study design, our outcomes merit further investigations in randomized controlled trials.

Disclosures

None of the authors has any conflict of interests with any company.

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