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A RANDOMIZED, DOUBLE-BLINDED, DOSE-RANGING STUDY OF BOTULINUM TOXIN BLADDER INJECTIONS IN THE TREATMENT OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME.

Hypothesis / aims of study: Interstitial cystitis/bladder pain syndrome (IC/BPS) remains a poorly understood and inadequately treated disorder. Botulinum toxin has proven effectiveness in patients with urgency-frequency due to detrusor overactivity but the safety and efficacy in patients with urgency-frequency due to pain remains unclear. Since botulinum toxin can block neurotransmitters other than acetylcholine (including common pain neurotransmitters) there is reason to think that it could be effective in patients with IC/BPS. Prior small, uncontrolled trials showed mixed results. The AUA Guideline Committee judged that botulinum toxin injections cannot be recommended "for general use for this disorder, but rather should be limited to practitioners with experience managing this syndrome and willingness to provide long-term care of these patients post intervention."[1]

We designed a single institution, double-blind, dose-ranging pilot trial in order to gather data that might be used to plan a proper phase II trial. We were interested in the feasibility of recruiting patients for office based therapy, finding a minimum dose that could produce clinical benefit, and assessing the risk of urinary retention.

Study design, materials and methods:
Eligible patients were adults diagnosed by the investigators with IC/BPS as the primary cause of their lower urinary tract symptoms. Symptoms were present for > 6 months and were refractory to standard therapies; current pain and urgency scores were ≥ 4/10 on a visual analogue scale. Cystoscopy with bladder distention under anesthesia was required at some point in the diagnostic evaluation. The NIDDK exclusion criteria were employed and residual urine >100cc was exclusionary. Prior Botox injection and neurostimulators were not allowed.

Subjects were randomized to one of 5 arms by drawing presealed envelopes. The arms were placebo, 50, 100, 150, and 200 units. Subjects were treated in a single session in clinic. Study drug was dissolved in 20cc normal saline and administered in 20 injections of 1cc in a 4-6-6-4 pattern distributed over the bladder, including 4 injections in the trigone. Injections were at the subepithelial level. Subjects were pretreated with 50cc 1% lidocaine in the bladder for 20 minutes prior to injection along with an oral narcotic and anxiolytic. They were given 3 days of a fluoroquinolone following the treatment.

Standard follow-up visits were at 1 and 3 months. The primary outcome measure was the patient Global Response Assessment (GRA) at 3 months—subjects self-rating "markedly" or "moderately" improved were defined as responders and all others as non-responders. The investigators and study coordinators were blinded to dosing assignments throughout. Subjects with poor outcome at 1 month were allowed to seek other treatment and were considered non-responders. Subjects who were responders at 3 months were followed to 6 months. Secondary outcome measures included VAS pain and urgency scores, the O'Leary-Sant Interstitial Cystitis symptom and problem indices, and 24 hour bladder diary variables.

Results
We recruited patients from a single tertiary care practice from May 2010 through August 2013. We enrolled 16 subjects (14 women and 2 men) with ages 24 to 88 years (mean 53.7). Recruitment was slow throughout; the study was stopped due to futility without reaching the target recruitment goal after eight months with no enrollment.

Only two subjects were randomized to placebo and the study was not designed to show differences between active treatment groups. The raw outcome data are presented in the Table following. Clear responses were seen in 4/14 subjects (28%) at the three month primary endpoint, all remained responders at 6 months. Two other patients could have been responders—one who was markedly better at one month and was lost to follow-up and a second who was moderately improved at one month who had a urinary tract infection at the 3 month assessment (best possible outcome 6/16, 38%). Catheter dependent urinary retention was seen in 5 subjects including one who rated herself a responder. Pain during the treatment was significant with 12/16 rating the pain ≥ 8/10. Three subjects continued to have pain at least 2 points higher than baseline 10 minutes after therapy was completed. There were no serious adverse events.

Patient	Gender	Age	Randomization	GRA 3 months	Urinary retention
001	Female	71.2	50	No change	No
002	Female	24.6	100	Markedly improved	No
003	Female	45.0	200	Moderately improved	Yes
004	Female	39.4	Placebo	Slightly improved	No
005	Female	39.7	150	No change	No
006	Male	56.0	100	Moderately improved	No

007	Female	53.3	200	Markedly worse***	Yes
008	Female	63.7	150	Withdraw--Non responder	No
009	Female	57.0	50	Withdraw--Non responder	No
010	Female	55.1	200	Slightly improved	No
011	Male	62.9	50	Slightly improved	No
012	Female	53.8	placebo	Withdraw--Non responder	No
013	Female	88.6	150	Responder--lost to follow-up	No
014	Female	69.7	100	Withdraw--Non responder	Yes
015	Female	32.1	100	Withdraw--Non responder	Yes
016	Female	47.8	100	Markedly improved	Yes

*** had urinary tract infection at the 3 month assessment

Interpretation of results: Botox bladder injections were effective for a minority of subjects with refractory IC/BPS; the response seen in this group of patients was lower than that reported in some uncontrolled case series. In addition, the rate of catheter dependent urinary retention was significantly higher than would be expected in a population of straightforward overactive bladder.

Concluding message: We concur with the current AUA Guidelines that Botox cannot be recommended for general use in IC/BPS. While some encouraging results have been reported in uncontrolled case series [2, 3] there remains a great deal to be learned about how best to employ this therapy. Carefully performed prospective randomized trials are necessary to define the best candidates with bladder pain and the optimal use of the treatment in the patient population. Significant barriers to recruitment for such studies include fear of retention/catheterization, fear of pain during treatment, and the increased access to Botox therapy outside of clinical trials.

References

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Disclosures

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