Botulinum A Toxin Intravesical Injection in Patients With Painful Bladder Syndrome: 1-Year Followup

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Purpose: We evaluated the 1-year efficacy and tolerability of botulinum A toxin intravesically injected in patients with painful bladder symptoms associated with increased urinary frequency, refractory to conventional treatments.

Materials and Methods: Three men and 12 women were prospectively included in the study. Under short general anesthesia the patients were given injections of 200 U commercially available botulinum A toxin diluted in 20 ml 0.9% NaCl. Injections were performed submucosally in the bladder trigone and lateral walls under cystoscopic guidance. A voiding chart and the visual analog scale for pain were used, and urodynamics were performed before treatment, and 1, 3, 5 and 12 months later.

Results: Overall 13 patients (86.6%) reported subjective improvement at the 1 and 3-month followups. The mean visual analog scale score, and daytime and nighttime urinary frequency were significantly decreased ($p < 0.05$, < 0.01 and < 0.05, respectively). At the 5-month followup the beneficial effects persisted in 26.6% of cases but increased daytime and nighttime urinary frequency, and an increased visual analog scale score were observed compared to baseline. At 12 months after treatment pain recurred in all patients. Nine patients complained of dysuria 1 month after treatment. Dysuria persisted in 4 cases at the 3-month followup and in 2 at the 5-month followup.

Conclusions: Intravesically injected botulinum toxin A is effective for short-term management of refractory painful bladder syndrome. The beneficial effects decreased progressively within a few months after treatment. Thus, repeat injections of the neurotoxin are required for efficacious treatment in patients with the disease.

Key Words: bladder; cystitis, interstitial; botulinum toxin type A; pain

Botulinum toxin type A is currently used to treat focal muscle overactivity and spasticity[1] as well as autonomic disorders such as hyperhidrosis.[2] Moreover, BoNT/A was recently introduced for the treatment of smooth muscle overactivity and several lower urinary tract dysfunctions.[3] In the last few years BoNT/A has also been used to treat a number of pain conditions. Pain diseases alleviated by BoNT/A encompass 2 main categories, including those related to muscle hyperactivity, including dystonia,[4] spasticity,[5] myofascial pain,[6] chronic pelvic pain[7] and tension-type headache, and those possibly related to neurovascular disorders, including migraine headache.[8] Pain related to spinal cord pathology has also been treated with BoNT/A.[9] The exact mechanism of the analgesic effect of BoNT/A is still poorly understood and it is possible that BoNT/A acts not only at the cholinergic terminals. In urology BoNT/A has been shown to have an antinociceptive effect on bladder tissue in animal chemical cystitis models[10] and in patients with painful bladder syndrome and interstitial cystitis.[3,11] The effect is likely to be mediated by the block of the release of several neurotransmitters involved in afferent nociceptive transmission.[12]

In a previous study we reported that BoNT/A intravesically injected in patients with painful bladder syndrome produced a beneficial effect on pain.[13] In that study the clinical effect was evaluated 1 and 3 months after single injection treatment. These results prompted us to perform a longitudinal study. In the current study we evaluated the 1-year efficacy and the tolerability of BoNT/A intravesically injected in patients with painful bladder symptoms associated with increased urinary frequency that were refractory to conventional treatment.

MATERIALS AND METHODS

The prospective study enrolled patients with refractory bladder pain and urgency-frequency syndrome in the presence of sterile urine. The study was approved by the local Ethics Committee and all patients provided written informed consent.

Inclusion and Exclusion Criteria

We included patients with refractory pain in the bladder and urethra, vagina or perineum during bladder filling or after micturition, who also complained of frequency, urgency and nocturia. Patients with neurological diseases, pregnancy and concomitant aminoglycoside use were excluded from study, together with patients with voiding difficulties and outlet obstruction due to urogenital prolapse or to diseases of the bladder neck and urethra. Patients who underwent

Submitted for publication June 6, 2007.
Study received local Ethics Committee approval.
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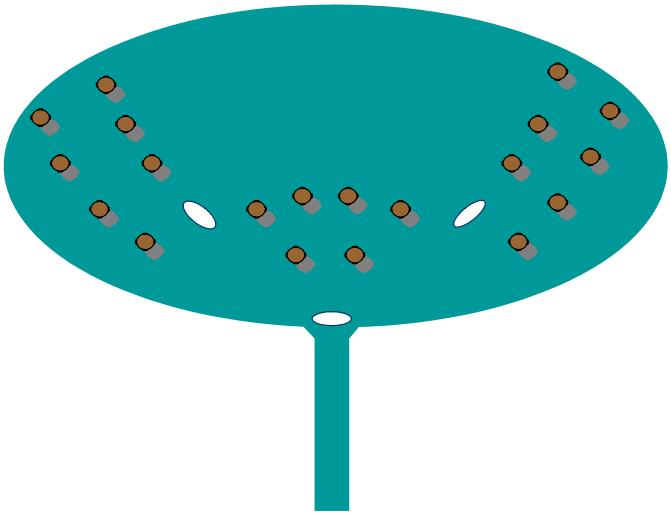
DOI:10.1016/j.juro.2007.10.032



Location and distribution of each single injection of 10 U BoNT/A in 1 ml normal saline (dark circles in diamonds) in bladder trigone and lateral walls in 15 patients with painful bladder symptoms.

prior radiotherapy or those with intravesical stones were also excluded. All previous treatments, including oral and intravesical therapies, had failed in all patients.

Baseline evaluation included a history, physical examination, serum chemistry, urinalysis, urine culture and imaging assessment of the upper and lower urinary tract. A voiding chart was used, cystoscopy was done and a VAS was used for pain quantification. Urodynamics following International Continence Society standards[14] were performed 1 month before commencing the study.

Study Plan and Treatment

A total of 15 patients fulfilling all criteria were selected and included in the study. While under short general anesthesia, the patients were injected with 200 U BoNT/A (Botox®) diluted in 20 ml 0.9% NaCl. Injections were performed through a rigid cystoscope using a flexible needle submucosally in the bladder lateral walls and trigone. The figure shows the schema of location and distribution of BoNT/A injections. A total of 10 U BoNT/A were used per injection site. After treatment a 16Ch Foley indwelling catheter was routinely inserted for 24 hours. Patients were discharged home after overnight observation and followed for bladder emptying and pain. Uroflowmetry with post-void residual volume measurements was performed after catheter removal.

Clinical evaluation, VAS, cystoscopy and urodynamics were subsequently repeated at 1, 3, 5 and 12 months. Local and/or systemic side effects were noted during and after treatment.

Data Analysis

Statistical analysis was performed using the Friedman, Wilcoxon and Mann-Whitney tests for nonparametric data. The Bonferroni correction was applied to post hoc multiple comparisons. Statistical significance was considered at $p < 0.05$. All data analyses were performed using SPSS®, release 10.1.1 for Windows®.

RESULTS

There were 12 females and 3 males with a mean ± SD age of 58 ± 9.9 years and mean disease history of 4.9 ± 2.4 years. All patients presented with increased daytime and nighttime urinary frequency, and pain in the bladder and urethra, vagina or perineum during bladder filling or after micturition.

Baseline

Mean daytime and nighttime urinary frequency was 15.2 ± 3.9 and 5.5 ± 1.5, respectively. The mean VAS score was 9.4 ± 0.9. The table lists clinical data.

On urodynamics all patients demonstrated abnormal bladder sensation (first desire to void less than 150 ml) in the absence of any uninhibited detrusor contraction. Mean cystometric capacity was 256.4 ± 33.5 ml and none of the patients showed impaired detrusor contractility. The table lists urodynamic data. At 24 hours after BoNT/A treatment 1 male and 2 female patients needed complementary intermittent catheterization due to a post-void residual volume of more than 150 ml.

One Month After Treatment

Mean daytime and nighttime urinary frequency was significantly decreased (7.9 ± 1.7 and 1.8 ± 1.5, $p < 0.01$ and < 0.05, respectively). Of the patients 13 (86.6%) reported a subjective improvement in bladder pain. Overall mean VAS score was 6.1 ± 2.4 ($p < 0.01$). Nine patients complained of different grades of dysuria and were able to void the bladder completely by abdominal straining. Furthermore, statistically significant improvements in urodynamic parameters were recorded. Mean maximum cystometric capacity increased from 256.4 ± 33.5 to 361.7 ± 48.4 ml ($p < 0.01$).

Clinical and urodynamic results before and after 200 U BonT/A intravesical injections in patients with painful bladder syndrome

	Mean ± SD Baseline	Mean ± SD 1 Mo	Mean ± SD 3 Mos	Mean ± SD 5 Mos	Mean ± SD 12 Mos	p Value
Frequency:						
Diurnal	15.2 ± 3.9	7.9 ± 1.7	8.7 ± 2.1	11.4 ± 1.3	13.3 ± 2.1	0.01
Nocturnal	5.5 ± 1.5	1.8 ± 1.5	2.4 ± 1.7	2.8 ± 1.5	3.9 ± 1.3	0.05
VAS score:						
All pts	9.4 ± 0.9	6.1 ± 2.4	6.8 ± 1.7	8.6 ± 0.2	8.8 ± 1.8	0.01
Pts on CIC	8.9 ± 1.9	6.4 ± 3.1	6.1 ± 3.0	8.3 ± 0.1	8.5 ± 2.0	0.01
Voiding diary urine vol (ml)	256.4 ± 33.5*	361.7 ± 48.4	325.7 ± 28.5	287.2 ± 16	275.6 ± 17.9	0.01
Max cystometric capacity (ml)	256.4 ± 33.5	361.7 ± 48.4	352.5 ± 50	305 ± 38	278 ± 28.9	0.01
Detrusor pressure at max urine flow (cm H_2O)	20.9 ± 18.6	13.2 ± 9.4	14.64 ± 11.2	17.6 ± 8.2	19 ± 12	0.05
Max urine flow (ml/sec)	21.2 ± 6.3	14.6 ± 13.1	15.5 ± 9.2	16 ± 13.4	18.7 ± 7.4	0.01