Prospective Randomized Evaluation of Periureteral Botulinum Toxin Type A Injection for Ureteral Stent Pain Reduction

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Abbreviations and Acronyms

BTX = botulinum toxin type A

UPJO = ureteropelvic junction obstruction

USSQ = Ureteral Stent Symptom Questionnaire

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Study received institutional review board approval.

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Purpose: The use of ureteral stents for ureteral obstruction and after ureteroscopy can result in substantial deterioration in patient quality of life due to pain, frequency and urgency. We postulated that many stent related symptoms may be related to detrusor muscle spasm in and around the intramural ureter, and evaluated the effect of botulinum toxin type A (Botox®) in patients with indwelling stents after ureteroscopy.

Materials and Methods: A total of 51 patients between December 2007 and March 2009 were enrolled in an institutional review board approved, prospective, randomized, single-blind study comparing botulinum toxin type A injection at a concentration of 10 U/ml to 3 locations around the ureteral orifice (30) vs no injection after unilateral ureteral stent insertion (21). Pain and urinary symptoms after stent placement were evaluated through the Ureteral Stent Symptom Questionnaire, which was completed on postoperative day 7. In addition, patients were required to maintain a log of narcotic use after stent placement until removal. The Wilcoxon rank sum and Fisher exact tests were used for nonparametric and categorical data, respectively, with $p \leq 0.05$ considered significant.

Results: No complications or adverse events occurred in this study. There was a significant decrease in the reported postoperative pain score between the botulinum toxin type A and control group at 3.4 vs 6.0 ($p = 0.02$). Postoperative narcotic use was also significantly less in the botulinum toxin type A group at 7.7 pills during an average of 2.7 days vs 24.7 in an average of 7.0 days in control patients ($p = 0.03$). With respect to postoperative lower urinary tract symptoms there was no significant difference between cohorts using the individual index scores within the Ureteral Stent Symptom Questionnaire. Stent related emergency room visits were reported by 1 patient treated in the botulinum toxin type A group vs 2 in the control group.

Conclusions: Periureteral botulinum toxin type A injection improves ureteral stent tolerability by significantly decreasing postoperative pain and narcotic requirements. Improvement in irritative symptoms was not observed.

Key Words: botulinum toxins, stents, ureter, pain

BOTULINUM toxin type A, derived from Clostridium botulinum, is a potent inhibitor of presynaptic acetylcholine release. Its function derives from its ability to cleave SNAP-25 protein, essential for synaptic vesicle fusion. This inhibition of acetylcholine release ultimately leads to the transient loss of neuronal activity in a targeted organ.[1] BTX was first approved for use in patients with strabismus and blepharospasm, and now has been im-

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plemented in urology to treat urinary urgency, frequency, incontinence and chronic pain syndromes.[2–5]

Indwelling ureteral stents have become an important part of the urological armamentarium and have been successfully used to treat obstructed ureters in many clinical settings. Despite their efficacy, ureteral stents are associated with significant morbidity including pain, frequency, urgency, dsyuria and hematuria.[6–8] Theories proposed to explain stent symptoms have included intrinsic reflux through the stent[9] or irritation induced by direct contract of the stent with the urothelium.[10] Numerous strategies have been used to decrease stent related symptoms including novel stent materials and designs, adjustment of stent length and diameter, and use of pharmaceuticals.[9,11,12] Despite these efforts, ureteral stent related morbidity remains a major challenge.

We postulate that many stent related symptoms may be caused by detrusor muscle spasm in and around the intramural ureter. Therefore, we evaluated the efficacy of ipsilateral periureteral BTX injection for the reduction of stent pain at ureteral stent placement.

METHODS

After obtaining institutional review board approval we performed a prospective, randomized, single-blind control study comparing periureteral BTX injection vs no injection after unilateral ureteral stent insertion. Between December 2007 and March 2009 a total of 51 patients 19 to 81 years old were incorporated in the study. All patients required a unilateral stent for benign pathology (nephrolithiasis, ureteral strictures, surveillance ureteroscopy etc). All patients signed informed consent before participating and were blinded to the randomization scheme.

Exclusion criteria were a history of malignancy, untreated urinary tract infections, benign prostatic hyperplasia, narcotic abuse or chronic pain disorders, detrusor overactivity, diabetes and neuropathy, as well as female patients who were pregnant, nursing or planning to become pregnant. In addition, patients with an anatomically or functionally solitary kidney, those with post-renal transplantation status and those who required antegrade stent placement were also excluded from the study protocol. All standard Food and Drug Administration contraindications and warnings for BTX injection were also in the exclusion criteria.

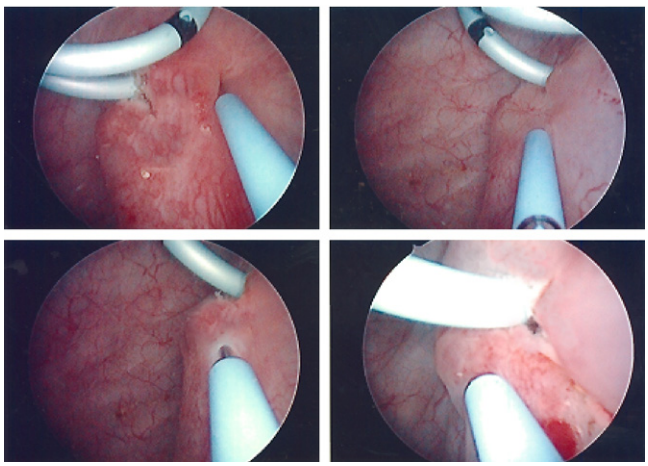
All patients completed a USSQ on postoperative day 7. The questionnaire evaluated the effect of ureteral stents on domains including urinary symptoms, body pain, general health, work performance, sexual function and any additional problems associated with stent placement. The scoring system of the USSQ is based on a simple sum of the scores of an individual question in each section. Each section has a numerical summary score in which a higher score is associated with a worse outcome. In addition, patients were asked to complete a daily narcotic log sheet documenting the amount and frequency of pain medication used until stent removal. All patients received a prescription for 40 pills of acetaminophen with oxycodone (325/5 mg) postoperatively and were asked to document whether additional pain medications were used. If patients required further pain medication they were asked to call the physician's office for a prescription renewal and these requirements were documented. The primary outcomes were based on the results of the USSQ and the narcotic log sheet.

Ureteral stent deployment was performed under fluoroscopic and cystoscopic guidance. After successful deployment of a standardized stent (6Fr multilength stents, Cook, Spencer, Indiana) patients randomized to the study group received 3 periureteral 1 ml injections of BTX at a concentration of 10 U/ml at 3 locations (total 30 units BTX). Injections were directed to the medial, lateral and inferior aspects of the ureteral office with the stent in place (see figure). Patients in the control group received no injection after stent deployment but were not informed of whether they did or did not receive an injection. All stents remained in position for a minimum of 7 days and were removed using flexible cystoscopy.

The Wilcoxon rank sum test was used to compare continuous variables including pain score and narcotic use. Fisher's exact test was used to compare categorical variables. A p value less than 0.05 was considered to be significant. All statistical analysis was completed using commercially available software.

RESULTS

Of 51 patients who provided consent, and were randomized to BTX and control groups, 40 (78.4%) returned the USSQ and 35 (69%) returned the narcotic log sheet at stent removal. With respect to demographic data the BTX and control groups were comparable (table 1). Average patient age was 48.1 years (range 19 to 81), and the overall distribution of male and female patients was 53% vs 47%, respectively. With respect to the indication for ureteral stent placement there was no significant difference



BTX injection sites