Long-Term Efficacy and Durability of Botulinum-A Toxin for Refractory Dysfunctional Voiding in Children

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Abbreviations and Acronyms

BTX-A = botulinum toxin A
DV = dysfunctional voiding
EUS = external urinary sphincter
HDN = hydronephrosis
LUTSS = lower urinary tract symptom score
PVR = post-void residual urine volume
Qmax = maximum flow rate
US = ultrasound
UTI = urinary tract infection
VCUG = voiding cystourethrogram
VUR = vesicoureteral reflux

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Purpose: We evaluated our long-term experience with intrasphincteric botulinum toxin A injection in children with dysfunctional voiding.

Materials and Methods: From January 2006 through July 2012 we saw 2,172 neurologically normal children due to dysfunctional voiding. Of patients who presented to these visits we retrospectively identified the charts of 12 with dysfunctional voiding (8 females) in whom urotherapy and medical management failed and who underwent botulinum toxin A injection to the external urinary sphincter. Mean patient age at surgery was 10.5 years (range 4 to 19). Average followup was 45 months (range 20 to 71). Preoperatively and postoperatively all children were evaluated with history and physical examination, voiding diary, renal and pelvic ultrasound with post-void residual volume measurement and uroflowmetry.

Results: Eight of the 12 children (67%) experienced significant improvement in voiding parameters. Before vs after treatment mean ± SD post-void residual urine volume was 115 ± 83 vs 57 ± 61 ml ($p = 0.016$) and the mean maximum flow rate was 11.8 ± 8.1 vs 20.4 ± 7.9 ml per second. Half of the cohort required a second injection an average of 15 months later. Three of the 4 patients who failed to show improvement had neuropsychiatric problems and 1 had evidence of bladder underactivity.

Conclusions: Our results demonstrate reasonable efficacy and durability of intrasphincteric botulinum toxin A injection in children with refractory dysfunctional voiding. Neuropsychiatric issues appear to negatively influence the success rate. Long-term followup is vital to identify patients in whom repeat injection may be necessary.

Key Words: urethra; botulinum toxins, type A; urinary incontinence; urinary tract infections; urination disorders

The first use of BTX-A injection to the EUS was reported in 1988 by Dykstra et al to treat detrusor-sphincter dyssynergia in spinal cord injured patients.[1] Since that time, BTX-A has been used to treat several types of neurogenic and nonneurogenic conditions in adults. These studies yielded a significant number of positive results, primarily decreased PVR.[2–7]

In 1997 Steinhardt et al were the first to report BTX-A use in a neurologically normal child with severe DV refractory to conventional treatment.[8] A total of 20 U were injected in 4 quadrants of the EUS along with urethral dilatation. The child was reportedly free of UTIs and had no further episodes of urinary incontinence 18 months later. Subsequently,

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a number of groups reported their experience with BTX-A injection for DV.[9–13] Although success rates are uniformly high, results are largely short term (6 months). Moreover, the injection technique, the BTX-A doses used and even the definition of success vary widely among these studies.

We evaluated our experience with BTX-A injection in the EUS in patients with DV after all standard treatment options failed. Specifically, we assessed the efficacy and durability of these results in the longer term to determine whether our initial positive results were sustained.

PATIENTS AND METHODS

Between January 2006 and July 2012 in a single outpatient pediatric urology office setting 2,172 neurologically normal children were diagnosed with DV. Data were prospectively collected and maintained in a database for this cohort at our institution since 2005. After obtaining institutional review board approval we retrospectively reviewed each patient chart and identified 8 males and 4 females who underwent 1 or more BTX-A injections to the EUS.

Presenting symptoms included urinary frequency or urgency, dysuria, idiopathic urinary retention, urinary incontinence and recurrent UTIs. Study participants were school-aged children between ages 4 and 19 years (mean 10.5). Evaluation consisted of medical history, physical examination and voiding diary. During an office visit parents completed 2 questionnaires, including a 21-question LUTSS and a 15-question psychosocial questionnaire.[13,14] All patients underwent screening urinalysis, uroflowmetry and pelvic US. Renal and bladder US, VCUG and/or spinal magnetic resonance imaging were done as clinically indicated. Demographic and health history data were collected, including age, gender, medical comorbidities, presenting symptoms, BTX-A amount and number of injections, PVR and uroflowmetry measurement.

Study inclusion criteria, ie reasons to be considered a candidate for EUS BTX-A injection, were failed standard urotherapy and continued evidence of DV. We previously reported our treatment algorithm for this patient cohort.[13] All children initially received behavioral modification taught by an experienced nurse practitioner. Constipation was assessed by history and pelvic US, and treated as warranted.

Patients in whom behavioral modification failed received secondary therapy consisting of oral medications (α-blockers or anticholinergics). Children with a component of incomplete emptying were initiated on α blockade. Those with urinary incontinence and complete emptying were initially started on anticholinergics. Those with persistent urinary incontinence after α-blocker therapy were started on anticholinergic therapy with α-blocker continued at the discretion of the provider. Children with no initial improvement with medication were referred to a licensed physical therapist with special training in pediatric pelvic floor rehabilitation. It was only after all of these therapies had been attempted that BTX-A treatment was offered. In all of these children repeat uroflow curves demonstrated a staccato or interrupted pattern with or without PVR measurements greater than 20% of expected bladder capacity.

Patients were excluded from study if they had a neurological disorder, or a congenital or other anatomical urological disorder responsible for DV. All children with known neuropsychiatric comorbidities were actively evaluated and/or treated during the observation period by a pediatric psychiatrist.

The injection technique in males consisted of a 23 gauge needle passed through the working channel of a 9.5Fr Storz® offset cystoscope. The EUS was visualized and injected at the 3, 6, 9 and 12 o'clock positions. In females the cystoscope was placed via the urethra. A 23 gauge spinal needle was inserted periurethrally and under direct vision 4 quadrants were injected at the mid urethra. The dose injected in all study patients was 100 U diluted in 4 ml saline (25 U/ml). Behavioral modification and physical therapy were again initiated 1 month after injection in all patients.

The followup protocol included patient interview and focused physical examination, urinalysis, uroflowmetry and pelvic ultrasound with PVR measurements at 1, 3, 6 and 12 months, and biannually thereafter. Evaluated post-injection parameters included medications, subjective symptomatology, culture proven UTIs, uroflowmetry, pelvic US and PVR measurement.

We defined treatment success as a 50% or greater improvement in presenting subjective symptoms and a statistically significant improvement in at least 1 objective parameter, eg flow rate or PVR measurement. Criteria for repeat injection in children were persistent difficult voiding and failure of objective improvement in noninvasive urodynamic testing results, ie the uroflow rate and PVR measurement.

Data were analyzed using standard statistical software with statistical significance considered at $p \leq 0.05$. Univariate analysis was performed using the paired Student t-test to compare mean $\pm$ SD values in the group.

RESULTS

Followup was between 20 and 71 months (median 45). Eight of the 12 children (67%) experienced significant improvement in voiding parameters and were considered to have achieved treatment success at the last followup visit (table 1). We performed a single injection in 6 of the 12 patients (50%) and 2 injections in the others. The average interval between repeat injections was 15 months (median 16.5). Five of the 6 patients (83%) who required repeat injection were considered to have achieved treatment success at last followup.

There were no acute complications, such as nausea, vomiting, dysphagia, respiratory depression or paralysis. In addition, no stress urinary incontinence was noted postoperatively. Two patients experienced 3 UTIs within the first week postoperatively. They were successfully treated with a

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