Clinical impact of botulinum toxin in detrusor sphincter dyssynergia management in pediatric patients with neurogenic bladder


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KEYWORDS
Detrusor sphincter dyssynergia;
Neurogenic bladder;
Botulinum toxin;
Mexico.

Abstract
Background: Detrusor sphincter dyssynergia (DSD) is characterized by the desynchronized activity of the detrusor muscle and the external urethral sphincter (EUS).
Aims: To evaluate the clinical response to the application of botulinum toxin type A for DSD in children with neurogenic bladder.
Material and methods: A descriptive, retrospective, cross-sectional study was conducted to evaluate the response to the application of botulinum toxin type A in DSD in children with neurogenic bladder.
Results: A total of 155 case records of urologic outpatients with neurogenic bladder were reviewed. Thirty-eight of them showed DSD. All received 100U of botulinum toxin type A in the EUS. The most frequent of the evaluated signs and symptoms were: urinary tract infection, total urinary incontinence, urinary urgency, hydronephrosis, diurnal leaks, and nocturnal leaks. After the application of botulinum toxin type A, we observed the following responses: urinary tract infections were resolved in 84.2% of the cases, total incontinence in 83.3%, hydronephrosis in 83.3%, urinary urgency in 66.6%, nocturnal leaks 16.6%, and diurnal leaks in 83.3%.
Conclusions: Botulinum toxin application in the EUS for DSD is a safe, effective, and reproducible option with favorable results.
Introduction

The bladder is a hollow viscus mainly composed of smooth muscle and whose basic functions are the storage of urine for periods of time and spontaneous emptying with voluntary control. Urine storage requires a reservoir with low pressure at maximum capacity and with voluntary control over continence. The emptying phase warrants voluntary control of the bladder sphincters and wall. Any alteration of neurologic origin in these functional phases of the bladder is generally known as neurogenic bladder. There are different types of neurogenic bladder, given that they involve a combination of distinct muscles in interaction. The neurogenic bladder is characterized by alterations of neurologic origin in normal bladder functions. They can manifest as difficulty in storing urine or in emptying the bladder.

Detrusor-sphincter dyssynergia (DSD) is a condition characterized by the simultaneous activity of the detrusor muscle and the external urethral sphincter (EUS). The most common symptom accompanying DSD is the uncoordinated and interrupted urinary stream. Urodynamic signs show an association between high micturition pressure and flow interruption, without altering the total emptying of the bladder. When evaluating small children with apparent micturition dysfunction, care must be taken not to interpret intermittent and transitory symptoms as pathologic ones, leading to unnecessary tests and studies. However, if the micturition dysfunction persists beyond the period of learning to control the sphincters, and especially if it is associated with urinary complications such as recurrent urosepsis, there can be anatomic and neurologic causes that must be studied.

The location of the neurologic lesion in DSD that causes the symptoms can be found at 3 different levels: above the brain stem, in the spinal cord, or in the peripheral nervous system. Among the multiple pathologies that affect the nervous system and that can manifest as symptoms at the lower urinary tract level are: cerebrovascular stroke, cerebellar ataxia, brain tumors, hydrocephalus, cerebral palsy, mental retardation, Parkinson’s disease, Shy-Drager syndrome, multiple sclerosis, myelodysplasia, sacral agenesis, spinal cord injury, diabetes, hemiated disc, infectious diseases -such as AIDS, Guillain Barré syndrome, herpes, human T-lymphotropic virus, Lyme disease, poliomelitis, syphilis, tuberculosis-, radical pelvic surgery -colorectal carcinoma resection and radical hysterectomy-, spinal cord surgery, medullar compression, and nonneurogenic neurogenic bladder as in the Hinman syndrome.

DSD is an illness that always warrants management. It is necessary to have a complete medical history that includes the interview, physical examination, neurologic examination, and laboratory tests and radiology studies. Finally, and as a fundamental part of the DSD patient evaluation, a complete urodynamic study should be carried out.

Botulinum toxin is produced by the Gram positive anaerobic bacterium Clostridium botulinum. It was first isolated in 1897 by van Ermengem and is one of the strongest neurotoxins known to humans. Structurally it is composed of a double amino acid chain of 150 kDa, made up of a light chain of 1897 kDa and a heavy chain of 50 kDa. It was first isolated in 1897 by van Ermengem and is one of the strongest neurotoxins known to humans. Structurally it is composed of a double amino acid chain of 150 kDa, made up of a light chain of 150 kDa and a heavy chain of 100 kDa, both connected by a disulfide bridge. Their action mechanism consists of inhibiting the release of acetylcholine in a presynaptic cholinergic junction. Although there are 7 immunologically distinct neurotoxins with different intracellular target proteins and different action characteristics, only the serotype A and B botulinum toxins have clinical use. Botulinum neurotoxin can inhibit the release of the sensory neuron neurotransmitters and result in peripheral desensitization. This neurotoxin can also block the central release of glutamate and reduce the excitatory amino acid receptors that are important in pain perception.
Clinical impact of botulinum toxin on detrusor sphincter dyssynergia

A descriptive, retrospective, cross-sectional study was conducted to determine the clinical impact of botulinum toxin type A in DSD management in pediatric patients with neurogenic bladder. The study universe was the patients seen at the Urology Service of the Instituto Nacional de Pediatría that were diagnosed with neurogenic bladder and DSD and treated endoscopically with botulinum toxin type A injection.

The following signs and symptoms were evaluated in the pre and post botulinum toxin application stages: urinary urgency, partial diurnal urine leaks, total urinary incontinence, acute urine retention episodes, urinary tenesmus, nocturnal urine leaks, and recurrent urinary infections. All patients had renal ultrasound, micturition cystourethrogram, and urinalysis, as well as uroflowmetry with electromyography of the EUS before and after botulinum toxin type A application.

Results

The case records of 155 patients seen at the Urology Service Outpatient Consultation, catalogued as neurogenic bladder, were reviewed. Thirty-eight patients showed DSD. Sixteen were males and 22 were females; mean age was 9.3 years (range from 1 to 19 years) (table 1). 100U of botulinum toxin type A in the EUS was applied to all the patients studied. The most frequent of the evaluated signs and symptoms was recurrent urinary infection with a total of 19 cases, followed by total urinary incontinence in 18, urinary urgency in 15, hydronephrosis in 12, diurnal urinary leaks in 12, and nocturnal urinary leaks in 12 patients (fig. 1) (table 2). After botulinum toxin application the following response was observed: urinary tract infection was resolved in 15 patients (84.2%), total incontinence in 15 (83.3%), hydronephrosis in 10 (83.3%), urinary urgency in 10 (66.6%), nocturnal leaks in 2 (16.6%), and diurnal leaks in 10 (83.3%) (table 3). Of the less frequent symptoms, acute urine retention and tenesmus were resolved in 100% of the cases, and urinary frequency in 50%.

The evaluated parameters during uroflowmetry were Q\text{max}, Q_{\text{mean}}, and micturition time and volume. In the stage before botulinum toxin application, the mean result in Q\text{max} was 14 mL/sec (1.9-35 mL/sec), the Q\text{mean} was 6.5 mL/sec (1.1-13.4 mL/sec), micturition time was 25 seconds (15-46 seconds), and the micturition volume was 75 mL (11-208 mL). After botulinum toxin application, the results were the following: Q\text{max} of 18.9 mL/sec (7.4-35.3 mL/sec), Q\text{mean} of 9.9 mL/sec (2.5-18 mL/sec), time of 15.8 seconds (5-31 seconds), and volume of 106 mL (50-196 mL) (table 4).

There were no side effects due to the drug in any of the cases.

Discussion

DSD is a micturition pattern in spinal cord injuries above the sacrum. It has critical consequences for the upper and lower urinary tract derived from the high intravesical pressures and post-micturition residues, as well as distressing symptoms for the patients such as urinary incontinence and dependency, and other potentially fatal ones such as dysreflexia episodes. Inadequate treatment can perpetuate this situation with devastating effects for the entire urinary tract. First line treatment for DSD patients consists of reducing the residues and intravesical pressures with intermittent catheters, as well as the involuntary contractions of the detrusor through the use of anticholinergic agents. Unfortunately, not all patients adhere to this treatment adequately for different reasons, ranging from difficulty in passing the catheter because of urethral trauma or manual disability, to medication intolerance. Some patients follow the treatment indications strictly and adequately, but despite their doing so, complications appear and often persist. Up to 50% of patients have symptomatic infections whose incidence becomes greater over time, and one third of men

<table>
<thead>
<tr>
<th>Table 1 Demographic characteristics</th>
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<tr>
<td>Mean age</td>
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<tr>
<td>9.3 years (range from 1 to 19 years)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male 16 (42.1%)</td>
</tr>
<tr>
<td>Female 22 (57.9%)</td>
</tr>
</tbody>
</table>

Since the first application of botulinum toxin type A in 1997 by Steinhardt for the treatment of DSD, its use has been extended to the treatment of children with neurogenic or nonneurogenic detrusor or sphincter hyperactivity that is resistant to conventional treatments. And since then, it has been used to treat children with treatment-resistant nonneurogenic detrusor hyperactivity and refractory micturition dysfunction. The duration of the induced paralysis varies depending on the type of muscle treated. In cases of hyperactivity of neurogenic and nonneurogenic detrusor hyperactivity, the treatment effect lasts from 10 to 12 months, and in the case of striated muscle, some 12 to 18 months. Myelomeningocele is the most common underlying pathology (93%) in the pediatric population affected by neurogenic bladder. The study universe was the patients seen at the Urology Service of the Instituto Nacional de Pediatría with neurogenic detrusor hyperactivity, followed by spinal cord tumors and trauma. First line treatments in the pediatric population include antimuscarinic drugs and clean intermittent catheterization. However, 10% to 15% of these patients present with refractory disease and severe adverse side effects.

The hypothesis for its use is that the period of paralysis of the pelvic floor musculature and the EUS after botulinum toxin injection is sufficient for correcting the incorrect micturition pattern and relearning the relaxation of the pelvic floor musculature, therefore utilizing standard urotherapy. Due to the great prevalence of bladder disease, the use of botulinum toxin for hyperactive bladder and detrusor hyperactivity has been more widely studied. Nevertheless, in the field of neurogenic and nonneurogenic DSD, botulinum toxin injection in the urethral sphincter or the pelvic floor continues to be a promising treatment.

The aim of the present study was to evaluate the improvement in symptoms and in uroflowmetry parameters in DSD management in pediatric patients with neurogenic bladder.
and 5% of women have long-term bleeding. Urethral narrowing increases with follow-up and the majority of cases present after the first 5 years; close to 15% of patients have urethral alterations that make catheterization difficult, 2% to 4% of them requiring surgical management.

Botulinum toxin type A has been used in DSD treatment for more than 20 years. Even though it is not the first line treatment method in these patients, it has become a very good option in those patients that are not candidates for or in whom other therapeutic methods have failed. This potent toxin, product of Clostridium botulinum, was initially approved for facial and esthetic use. Today, we urologists have adopted it not only for uncoordinated micturition, but also for the treatment of detrusor hyperactivity, interstitial cystitis, urinary retention, and prostate pathologies; with good results despite the fact that its application in the lower urinary tract has not been approved by the FDA.

Even though it is a minimally invasive procedure with an excellent safety profile, there have been reports of irritative micturition symptoms or hematuria, as well as rare reports of generalized weakness, dysphagia, diplopia, blurred vision, dry mouth, and general malaise. In our case series there were no major complications.

In general, we have observed a notable improvement in symptomatology and recurrent infections, similar to that reported in the medical literature, as well as an improvement in the uroflowmetry pattern after the application of botulinum toxin in the EUS.

A limitation of our study is the fact that it was a retrospectively analyzed case series. However, its principal merit is that it is the largest case series reported on in the Mexican medical literature.

Conclusions

Botulinum toxin application in the EUS as DSD treatment is a technically reproducible, effective, and safe option, with favorable results for the control of symptoms and the re-establishment of the functional imbalance, having an effect on upper urinary tract function.

Financial disclosure

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### Table 3 Symptom improvement percentage

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Percentage</th>
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<tr>
<td>Recurrent UTI</td>
<td>84.2%</td>
</tr>
<tr>
<td>Total urinary incontinence</td>
<td>83.3%</td>
</tr>
<tr>
<td>Urgency</td>
<td>66.6%</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>83.3%</td>
</tr>
<tr>
<td>Diurnal urine leaks</td>
<td>83.3%</td>
</tr>
<tr>
<td>Nocturnal leaks</td>
<td>16.6%</td>
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</tbody>
</table>

UTI: urinary tract infection.

### Table 4 Resultados de urofluometría

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before botulinum toxin application</th>
<th>After botulinum toxin application</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_{max}$</td>
<td>14 mL/sec</td>
<td>18.9 mL/sec</td>
</tr>
<tr>
<td>$Q_{mean}$</td>
<td>6.5 mL/sec</td>
<td>9.9 mL/sec</td>
</tr>
<tr>
<td>Time</td>
<td>25 sec</td>
<td>15.8 sec</td>
</tr>
<tr>
<td>Volume</td>
<td>75 mL</td>
<td>106 mL</td>
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### Conflict de interés

The authors declare that there was no conflict of interest.

### References