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Botulinum toxin injection in the pediatric population with medically refractory neuropathic bladder

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Summary

Introduction
Botulinum toxin injection (BTI) has been advocated as a second line therapy in management of neuropathic bladder in pediatric population for refractory patients to conventional medical management such as anticholinergics. The purpose was to review the safety and efficacy of BTI in children with neuropathic bladder refractory to conservative non-surgical measures. We hypothesized that BTI would be an effective alternative to bladder augmentation in certain patients but not all.

Methods
We retrospectively identified 22 patients with neuropathic bladder due to any condition who underwent urologic BTI at our hospital since 2010. Multiple clinicopathologic variables were examined including the following: demographics, use of anticholinergics, the presence of anticholinergic refractoriness or intolerance, dosage of BTI, urodynamic variables, and continence status.

Results
The mean patient age at time of BTI was 10 years with a follow up of 12 months. Indications for BTI were anti-cholinergic refractory (AR) urodynamic parameters and/or incontinence and anticholinergic intolerance (AI). Nearly all patients received 300 Units at BTI into detrusor. No complications occurred from BTI. Overall 54% had improved continence after the initial BTI whereas 45% had achieved complete continence between catheterizations. Cystometric capacity increased by 46% and maximum detrusor pressure decreased by 43% following initial BTI (See Table). 75% of AI patients were continent between CIC after BTI compared to 50% of AR patients ($P = 0.002$). The observed mean duration of clinical improvement after initial BTI was 4.6 months and four patients underwent repeat BTI. ***Pre BTI % of age expected bladder capacity Post BTI % of age expected bladder capacity % Improvement in Urodynamic Parameter P value Cystometric Capacity (mL)*** **227 60 331 87 46 0.008** ***Maximum Detrusor Pressure (cm H_2O)*** **63 44 43 0.002** ***Compliance (mL/cm H_2O)*** **4.3 8.8 104 0.001**.

Discussion
Our results are comparable to existing literature with respect to urodynamic parameters. The observed differences may be due to heterogenous patient population of various etiologies of neuropathic bladder and no uniform criteria to proceed with bladder augmentation. The AR patients in our cohort may have had a higher degree of bladder fibrosis which BTI would be less likely to impact and explain the differences in clinical response between AR and AI patients.

Conclusions
BTI is a safe and effective treatment option for pediatric patients with neuropathic bladder refractory to standard therapy. The degree of continence observed after BTI in our series was higher for AI rather than AR patients.

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Table Urodynamic changes following Botulinum toxin injection.

	Pre-Botulinum toxin injection	% of age-expected bladder capacity	Post Botulinum toxin injection	% of age-expected bladder capacity	% improvement in urodynamic parameters	*P*-value
Cystometric capacity (ml)	227	60	331	87	46	0.008
Maximum detrusor pressure (cm H_2O)	63		44		43	0.002
Compliance (ml/cm H_2O)	4.3		8.8		104	0.001
Uninhibited detrusor contractions (UDC)	14/22 (63% of total patients)		4/14 (29% of patients with UDC pre-BTI)			

Introduction

Neuropathic bladder can be associated with increased intravesical pressures, which if left untreated and are persistent, pose potential risk to the upper urinary tract. Neuropathic bladder can also cause urinary symptoms and incontinence that can be detrimental to the patient's health-related quality of life [1,2]. Oral anticholinergics have widely been used as a first-line treatment for patients with neuropathic bladder with CIC. However, anticholinergics can either be ineffective or cause undesirable systemic side effects, leading the patient to their discontinuation [3,4]. The goals of treatment in patients with neuropathic bladder are to protect from renal damage, minimize the risk of UTI, and achieve urinary continence. If anticholinergics and CIC do not provide the desired result when implemented, it may be necessary to pursue secondary therapeutics and/or surgical intervention [5].

Botulinum toxin (BT) is a neurotoxin produced by the facultative anaerobe *Clostridium botulinum*, which acts on the peripheral nervous system to block the release of acetylcholine from presynaptic nerve endings. It temporarily paralyzes the target organs and modulates afferent pathways [6]. Botulinum toxin injection (BTI) has been advocated as a therapeutic alternative to bladder augmentation in the pediatric population with neuropathic bladder [1,7]. Botulinum toxin reliably diminishes external sphincter and detrusor overactivity when injected into the external urethral sphincter and detrusor, respectively [8,9]. Previous reports have described that the efficacy of a single BTI decreases with time, and reinjection is usually necessary to sustain its clinical effect [10,11].

The goal of the present study was to describe the present institution's experience of the safety and efficacy of BTI in children with neuropathic bladder refractory or intolerant to conservative medical measures.

Materials and methods

A retrospective review was performed of pediatric patients with neuropathic bladder who underwent urologic BTI over a 5-year period (2010–2014). Patients who underwent BTI to the urethral sphincter alone ($n = 3$) for treatment of idiopathic urinary retention were excluded, as no neurological cause for bladder external urethral dyssynergia was found.

All patients were on CIC, and underwent urodynamic assessment prior to BTI as part of the standard of care management of neuropathic bladder. All patients had been tried on anticholinergics prior to BTI. The most commonly used anticholinergic was oxybutynin, with maximum prescribed dosages of 0.3–0.4 mg/kg. During urodynamics, detrusor compliance was defined as the delta of bladder volume (ml) over the delta of detrusor pressure (cmH_2O). In order to calculate this, the difference of these parameters at the beginning of bladder filling and cystometric capacity were looked at. Bladder capacity was estimated for age using the formula:

$$\text{Age expected bladder capacity (ml)} = [\text{age (years)} + 2] \times 30.$$

In all patients, BTI was performed under general anesthesia with rigid cystoscope and an endoscopic needle. Botulinum toxin was diluted with normal saline to a concentration of 10 units/ml, and a small amount of methylene blue was added to identify the injection sites. Approximately 10 units were injected into the detrusor along the posterior and lateral walls, while sparing the trigone. The dose of BT that was injected was 10 units/kg, with a maximum of 300 units administered.

Multiple clinicopathologic variables were retrospectively examined, including the following: age, sex, etiology of neuropathic bladder, the presence of anticholinergic refractoriness or intolerance, length of time on anticholinergics, dosage of BTI, urodynamic variables before and 3 months after the BTI, and urinary continence status. Anticholinergic intolerance was defined as the patient's discontinuation of anticholinergic medication due to persistent side effects (i.e. dryness of mouth, constipation, hot flushes, etc.) documented in the medical records. Anticholinergic refractoriness was defined as the inability to attain the desired clinical effects, based upon the continence and/or urodynamic variables, despite maximum tolerable dose of anticholinergics. The maximum tolerable dose of anticholinergics was determined by unwillingness of the patient, family or physician to accept dosage escalation due to side effects attributed to anticholinergics, such as dry mouth, facial flushing, constipation and/or behavioral or cognitive changes observed. Patients were considered continent if there were no documented wet diapers or urinary leakage between prescribed intervals of CIC of every 3–4 h. Continence was assessed by retrospective review of parental reports at the time of clinic visit.