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Outcomes of Intradetrusor OnabotulinumtoxinA Injection in Adults with Congenital Spinal Dysraphism in Tertiary Transitional Urology Clinic

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Abstract

Purpose—Published data regarding intradetrusor injection of onabotulinumtoxinA in adults with congenital spinal dysraphism are scarce. In this study, we retrospectively investigated the outcomes of intradetrusor injection of onabotulinumtoxinA in this setting.

Materials and Methods—Billing codes were used to identify 149 patients who underwent onabotulinumtoxinA injection between 2012–2016 at our tertiary transitional urology clinic. Charts were then reviewed to identify patients with congenital spinal dysraphism.

Results—A total of 18 patients with the mean age of 20.76 (± 3.03) years at the time of 1st onabotulinumtoxinA injection were identified. All patients had urinary incontinence. Urinary incontinence improved by injection of 200 or 300 U of onabotulinumtoxinA in 81.2% of patients and 63.6% of them became dry ($p = 0.023$). Mean glomerular filtration rate before and 13.3 (± 9) months after treatment was 100.2 (± 17.2) and 120.1 (± 16.6) mL/min/1.73 m² respectively ($p = 0.41$). Baseline hydronephrosis improved in 3 of 4 patients. Repeat urodynamic study after injection was done in 11 patients who did not clinically improve or who had loss of bladder compliance at baseline (29.3 Vs. 67.2 ml/cmH₂O). Mean maximum cystometric capacity before and after injection was 310.1 and 380.2 mL ($p = 0.045$). Mean bladder compliance before and after treatment was 29.2 and 28.7 ml/cmH₂O respectively ($p = 0.48$) in this high risk group.

Conclusions—Intradetrusor onabotulinumtoxinA injection may improve refractory urinary incontinence in selected adults with spinal dysraphism. However, despite improvement in maximum cystometric capacity, bladder compliance does not improve following therapy in patients who had loss of compliance at baseline.

Background

Spinal dysraphism, such as spina bifida, may lead to paralysis of the legs and incontinence of urine and stool ¹. Although, major reconstructive urological surgeries still have an important role in managing these patients ², over the past few decades much progress has

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been made to improve urinary incontinence (UI) in these patients using conservative modalities such as clean intermittent catheterization and medications³. Some patients do not respond to oral medications or their neurogenic constipation can be worsened by the anticholinergic side effects. Intradetrusor injection of onabotulinumtoxinA (OnabotA) has been used by various groups to delay or avoid the need for augmentation cystoplasty⁴. Nevertheless, almost all published studies regarding intradetrusor injection of OnabotA in patients with spinal dysraphism have been done in pediatric or adolescent age groups⁵. Studies regarding onabotulinumtoxinA efficacy in adults with congenital spinal dysraphism which might present with more advanced disease with a fibrotic bladder and decreased bladder compliance are lacking. The strongest data supporting using onabotulinumtoxinA in neurogenic detrusor overactivity (NDO) in adults comes from DIGNITY clinical research program which only recruited patients with multiple sclerosis and spinal cord injuries^{6,7}. Despite some similarities to multiple sclerosis and spinal cord injury patients, adult patients with congenital spinal dysraphism, represent a distinct group of patients with neurogenic bladder. We hypothesized that although OnabotulinumtoxinA has some clinical efficacy in adults with congenital spinal dysraphism, a substantial number of patients would not benefit from this intervention due to their advanced bladder disease.

Methods

Billing codes were used to identify 149 patients who underwent OnabotA injection in the clinic or the operating room between 2012 and 2016 at our tertiary transitional urology clinic. Charts were reviewed to determine which patients had any form of congenital spinal dysraphism. Detailed retrospective chart review was performed before and after intradetrusor OnabotA injections to explore outcome of this treatment for UI. Our current institution policy is to start with intradetrusor injection of OnabotA 200U and increase to 300U if it fails (low response or early deterioration of response) in NDO setting when patients have failed anticholinergics or unable to tolerate the medications. In this retrospective study five injections of Botox 300U were done in two patients in 2014 based on the physician discretion. All other patients received 200U throughout the study period. Intradetrusor injection of OnabotA was performed in clinic under local anesthesia when possible and in the operating room when access to the bladder was limited. 20 or 30 injections were administered cystoscopically throughout the bladder, including the trigone. In the setting of augmentation cystoplasty, injections were performed into the native bladder and the augment (only 3-5 injections in the augment section). Repeat video-urodynamic study (VUDS) after initial OnabotA treatment was done if the patient had persistent or unchanged incontinence and/or was "high risk" defined as patients with decreased bladder compliance (less than 20 ml/cmH₂O), presence of vesicoureteral reflux (VUR), worsening renal function or hydronephrosis. Comparison between clinical and urodynamic findings was accomplished before and after intradetrusor injection of OnabotA. Statistical analysis using STATA 14 was performed by t-test and McNemar's Chi-squared tests for comparing 2 dependent means and 2 paired categorical data respectively.

Results

A total of 18 patients (8 males and 10 females) with congenital spinal dysraphism and UI were identified with a mean age of 20.76 (± 3.03) years at the time of first OnabotA injection. Seventeen (94.4%) of patients were performing Clean Intermittent Catheterization at baseline. The urological history of patients has been summarized in the Table 1.

A total of 57 OnabotA injections (200 and 300 U in 52 and 5 injections respectively) were performed in this patient population with refractory UI. The mean number of OnabotA injections was 3.1 (± 1.7) times. Mean interval time between injections was 7.23 months.

All patients had UI through their native urethra or their stoma at baseline. UI improved with OnabotA injection in 81.2% of patients and 63.6% of them became completely dry ($p=0.023$). After excluding one patient with end stage renal disease who needed renal transplantation at baseline, mean glomerular filtration rate (GFR) before and 13.3 (± 9) months after treatment was 100.2 (± 17.2) and 120.1 (± 16.6) mL/min/1.73 m² respectively ($p=0.41$). Hydronephrosis improved in 3 of 4 (75%) patients who had follow-up ultrasound while it did not change in the other patient (25%). Pre-treatment bladder compliance in the patient in whom degree of hydronephrosis did not improve was 10.8 ml/cmH₂O. This finding is in contrast to the patients in whom the hydronephrosis improved where mean bladder compliance was 44.3 (± 14) ml/cmH₂O.

Repeat UDS after OnabotA injection was done in 11 (61.1%) patients who had persistent or unchanged UI or were categorized as “high risk” as defined in methods section. Maximum cystometric capacity (MCC) improved following OnabotA injection from 310.18 (74.12) to 380.27 (107.37) mL ($p=0.045$). Neurogenic detrusor overactivity was observed in 62.5% and 50% of patients before and after treatment ($p=0.5$). Mean bladder compliance in 6 (33.3%) patients with decreased baseline compliance before and after treatment was 8.97 (± 2.71) ml/cmH₂O and 18.1 (± 12.7) respectively ($p=0.11$).

Regarding vesicoureteral reflux, our cohort had seven patients with low grade vesicoureteral reflux at baseline (Grade 1-2). Mean compliance in this group was 23.58 (range of 6.8-64.3). Mean compliance post treatment in the VUR group was 26.15 (range 10.3-52.8). Presence of “pop-off” mechanisms such as high grade VUR into dilated upper urinary tracts may hinder appropriate bladder compliance measurement.^{8,9} However, in our cohort vesicoureteral reflux was mainly grade 1 and 2 and possibly its effect on pressure measurements during filling was minimal.

Discussion

Spinal dysraphism encompasses a spectrum from tethered cord to spina bifida to sacral agenesis with spina bifida being the most common type. Spina Bifida is estimated to occur in 3.1 per 10000 children and adolescents 0 to 19 years of age and 3.3 per 10000 adolescents 16 to 19 years of age in the United States.¹⁰ The goals of urological management in neurogenic bladder patients with spinal dysraphism include protection of renal function, bladder and bowel continence and improving quality-of-life.³ With transition to adulthood, more attention is directed to urinary and bowel continence.¹¹

Reconstructive surgeries have been the most successful option in the management of UI in this setting. However, they are invasive, costly and complications are common³. First, conservative modalities are considered including clean intermittent catheterization and oral medications. Some patients do not respond to oral medications or their neurogenic constipation is worsened by medication side effects and intradetrusor injection of various forms of botulinum toxin A (onabotulinumtoxinA and abobotulinumtoxinA) has been used in children with refractory UI⁴. In a small subset of patients, these goals are not achieved or do not last long term following the reconstructive procedures such as augmentation cystoplasty and there is little guidance on how to proceed next. Traditionally, if conservative measures such as anticholinergics and clean intermittent catheterization fail, repeat augmentation is performed.¹² However, OnabotA injection may represent a less invasive option and it was applied to a subset of our patients in this cohort.

A systematic review was performed by Hascoet and colleagues¹³ in 2016 which included 12 studies and 293 patients who were all younger than 18 years of age. Complete resolution of incontinence occurred in 32 to 100% of patients^{13–24} MCC increased from 27 to 162% in different studies^{13–17,19–22,24,25}. Two studies implied that botulinum toxin A has lower efficacy in patients with low bladder compliance^{13,16,23}

To our knowledge, there have been no reports on the intradetrusor use of OnabotA injection in adult patients with congenital spinal dysraphism, representing a distinct group of patients with neurogenic bladder dysfunction¹³. Our study, which specifically focuses on adults with spinal dysraphism and mean age of 20.76 (± 3.03) years at the time of the initial OnabotA injection, showed UI improved by OnabotA injection in 81.25% of patients and 63.66% of them became dry. Mean MCC, which might have a role in patients' dryness, also improved significantly with the treatment.

The other goal was preservation of renal function in this setting. Our short term follow-up data shows that mean GFR was stable and hydronephrosis improved in most patients who had hydronephrosis before treatment. However, hydronephrosis did not improve in one patient with baseline decreased compliance of 10.8 ml/cmH₂O.

Our study shows that compliance may not improve with OnabotA injection in adult patients with decreased compliance at baseline which is consistent with prior studies in children. In a study done by Horst and colleagues, bladder compliance did not improve with OnabotA injection in 10 of 11 children with neurogenic bladder who had poor baseline compliance¹⁶. Tiryaki and colleagues also concluded that botulinum injection is useless in fibrotic neuropathic bladders with poor baseline compliance²³.

Limitations of our study include the retrospective nature of this study with small numbers of patients and a relatively short follow-up. Additionally, we only had available eGFR (calculated based on serum creatinine) which is a poor marker to assess renal function in this patient population, who often have decreased overall muscle mass.²⁶ Accruing large number of adult patients with this congenital spinal dysraphism is difficult in most centers even in tertiary centers with large number of referral of neurogenic bladder patients, thus highlighting the need for multicenter investigations in the future. It appears that earlier

intervention with OnabotA at a younger age in patients with spinal dysraphism, before significant bladder remodeling and loss of compliance, may be more beneficial. Single-center data such as the current cohort may limit our understanding of this important issue. Future prospective and multicenter trials are needed to better evaluate the effects of OnabotA in adults with spinal dysraphism and UI.

In conclusion, Intradetrusor OnabotA injection may improve refractory UI in adults with spinal dysraphism. However, despite improvement in MCC, bladder compliance may not improve following therapy in patients who had loss of compliance at baseline. Earlier intervention might be more beneficial in this specific patient population.

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Key of Definitions for Abbreviations

MCC:	Maximum Cystometric Capacity
NDO:	neurogenic detrusor overactivity
OnabotA:	onabotulinumtoxinA
UDS:	Urodynamic Study
UI:	Urinary Incontinence

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Table 1.

Patients' urological history

History		Values
Diagnosis	Myelomeningocele, No (%)	14 (77.7%)
	Sacral Agenesis, No (%)	2 (11.1%)
	Spina Bifida Occulta, No (%)	1 (5.5%)
	Tethered Cord, No (%)	1 (5.5%)
Bladder Management	Augmentation Cystoplasty, No (%)	5 (27.7%)
	Continent Catheterizable Channel, No (%)	6 (33.3%)
	Channel without Augmentation Cystoplasty, No (%)	3 (16.6%)
	On Clean Intermittent Catheterization, No (%) ^{a)}	17 (94.4%)
Clinical Finding	Spontaneous Voider, No (%)	1 (5.5%)
	Refractory UI (Urethra or Channel), No (%)	18 (100%)
	Mean GFR before Treatment, mL/min/1.73 m ² ^{b)}	100.2 (±17.2)
	Hydronephrosis before Treatment, No (%)	5 (27.7%)
	UDS before Treatment, No (%)	18 (100%)

No, number; UI, urinary incontinence; GFR, glomerular filtration rate; UDS, urodynamic study

^{a)}Through urethra or channel

^{b)}Excluding one patient with end stage renal disease who needed renal transplantation at baseline