Journal of Pediatric Urology (2014) 10, 368–373

Journal of Pediatric urology

Single-center experience with botulinum toxin endoscopic detrusor injection for the treatment of congenital neuropathic bladder in children: Effect of dose adjustment, multiple injections, and avoidance of reconstructive procedures

V. Figueroa [a], R. Romao [a], J.L. Pippi Salle [a], M.A. Koyle [a], L.H.P. Braga [b], D.J. Bägli [a], A.J. Lorenzo [a,*]

[a] *Division of Urology, The Hospital for Sick Children and University of Toronto, 555 University Avenue, Toronto, ON M5G 1X8, Canada*
[b] *Division of Urology, McMaster Children's Hospital and McMaster University, Hamilton, ON, Canada*

Received 29 April 2013; accepted 16 October 2013
Available online 7 November 2013

KEYWORDS
Neuropathic bladder;
OnabotulinumtoxinA;
Intravesical drug administration;
Incontinence;
Children

Abstract *Objective:* Since 2007, intra-detrusor OnabotulinumtoxinA (OnabotA) injections have been selectively offered at our institution for cases in which maximal anticholinergic therapy failed or was not tolerated. Herein we present our experience with this approach.
Materials and methods: We prospectively obtained data on 17 patients who underwent OnabotA injections over a 4-year period. Demographic information, number of injections, and dose delivered were captured. Children were monitored with baseline and post-injection renal ultrasound, urodynamics, and assessed for side effects, satisfaction, and symptom improvement.
Results: Forty-three sessions were performed with injections given every ~6 months. Mean patient age was 10.7 years (range, 3–17). Compared with baseline, after the first injection, mean bladder capacity adjusted for age and compliance improved by 27% ($p = 0.039$) and 45.2% ($p = 0.041$), respectively. After subsequent injections, these values increased to 35.7% ($p = 0.043$) and 55.1% ($p = 0.091$), respectively. Out of 13 symptomatic patients, $\geq$ 50% improvement was reported in ten (76.9%) and complete resolution in seven (53.8%). However, all three patients in whom the maximum dose of OnabotA was reduced from 300 to 200 units complained of recurrent symptoms. Fourteen children avoided surgical reconstruction as a second line of treatment. Overall patient/parental reported satisfaction rate was 70.6% (12/17).

* Corresponding author. Tel.: +1 416 813 6465; fax: +1 416 813 6461.
E-mail address: armando.lorenzo@sickkids.ca (A.J. Lorenzo).

http://dx.doi.org/10.1016/j.jpurol.2013.10.011

Conclusions: Intra-detrusor OnabotA injection is a promising intervention for management of neuropathic bladder in selected patients. Our data demonstrate improvement in symptoms and urodynamic parameters. Although an optimal dose has not been determined for children, we found optimal response with a maximum administration of OnabotA up to 300 units.

Introduction

Congenital neuropathic bladder (CNB) is a dynamic condition that can be associated with upper urinary tract deterioration in children and adolescents. Important factors that can lead to these adverse outcomes include elevated bladder storage pressures and poor bladder emptying [1,2]. The two main objectives in managing patients with CNB are to avoid renal compromise and reach social urinary continence through the least invasive and most effective approach. Currently, the combination of clean intermittent catheterization (CIC) and anticholinergic therapy (ACT) is considered the first line of treatment to reduce detrusor over-activity, and attain low intravesical filling pressures and age-appropriate bladder capacity, while achieving regular urine evacuation [3]. Unfortunately, ACT is either ineffective or triggers important side effects in about 10% of patients [4]. In these cases, bladder augmentation (BA) is considered, accepting the morbidity related to the procedure and side effects from constant exposure of intestinal mucosa to urine and mucous production with consequent development of bladder stones [5]. Indeed, although a rather life-altering surgical solution to the problem, BA has been associated with important short-and long-term complications [6].

OnabotulinumtoxinA (OnabotA) is one of the most potent known natural neurotoxins, exerting many of its actions by blocking the release of acetylcholine into the synaptic gap of the neuromuscular junction, decreasing substance P and calcitonin-gene-related peptide release in afferent nerves, and modulating the expression of vanilloid subfamily 1 and purinergic receptor P2X in the bladder wall [7–9]. Ultimately, OnabotA results in temporary paralysis of the target organ and modulates afferent pathways. To that purpose, it has been introduced into clinical practice, including management of urological conditions. Intra-detrusor injections (IDI) with botulinum toxin were first reported by Schurch et al. for treatment of neuropathic bladder dysfunction in teenage and adult spinal cord injury patients, being subsequently employed in the pediatric population following the landmark publication by Schulte-Baukloh in 2002 [10]. Since then, this novel pharmacological manipulation has gained increasing popularity within the therapeutic armamentarium of options for lower urinary tract dysfunction management in adults and—successively—children, thus far enjoying a favorable side effect and safety profile [5,11–13]. As the worldwide experience grows, concerns regarding long-term efficacy and optimal dosing scheme have been rightfully raised. Herein, we evaluate the effect of OnabotA IDI along with the effect of dose adjustment, multiple injections, and avoidance of lower urinary tract reconstruction on a select pediatric patient population considered for more aggressive surgical management. We hypothesized that OnabotA IDI would provide urodynamic and clinical improvement, sustained over time with regular re-injections.

Materials and methods

Following approval by our research ethics board, we collected data on 17 patients with CNB secondary to spina bifida/spinal dysraphism and tethered cord, who were prospectively offered IDI with OnabotA over a 4-year period under an institutional innovation initiative. Only patients with at least one post-injection follow-up visit were included. In all cases, injections were performed under general anesthesia using a rigid 9.5-Fr cystoscope with a straight working channel. OnabotA (Botox; Allergan, Irvine, CA, USA) was exclusively employed, diluted in normal saline to a concentration of 10 units/cc, following the manufacturer's directions. Equally distributed doses were administered with an endoscopic injection needle into the detrusor muscle, sparing the trigone, for a total dose of 10 OnabotA units/kg up to a maximum of 300 units. During the study we offered maximum dose adjustment based on emerging data from published evidence (randomized controlled trials in adults), thus some patients were subsequently offered the option to receive IDI up to a maximum of 200 units.

Patient demographic information, number of injections, and dose of OnabotA employed were captured. Children were monitored with baseline and 12-week post-injection renal ultrasound, urodynamic studies (UDS), and assessed for side effects, satisfaction, and symptom improvement. The use of ACT, request to remain in the injection program, and desire to proceed with BA were recorded during follow-up.

During UDS, detrusor compliance was defined as the delta of bladder volume (ml) over the delta of detrusor pressure (cmH_2O). In order to calculate this, we looked at the difference of these parameters at the beginning of bladder filling and maximum bladder capacity. Both points were measured in absence of concurrent detrusor contractions. Bladder capacity was adjusted for age using the formula described by Koff [14]: Bladder capacity (ml) $=$ [age (years) $+$ 2] $\times$ 30.

Categorical variables are presented as proportions, and continuous variables are summarized as means with SDs. Fisher's exact and Chi-square tests were used to compare differences in proportions for the outcome of interest. Continuous variables contrasting patients against his/her baseline values (pre- and post-injections) were analyzed with paired *t*-tests. A *p*-value of $\leq$0.05 was considered as statistically significant.

Results

Over the study period 43 sessions of OnabotA were conducted in 17 patients, with injections offered every 6