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Intradetrusor Injections of Onabotulinum Toxin-A in Children With Urinary Incontinence due to Neurogenic Detrusor Overactivity Refractory to Antimuscarinic Treatment

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Purpose: This was a prospective single-arm study to assess the efficacy and safety of intradetrusor injections of onabotulinum toxin-A in children with urinary incontinence associated with neurogenic detrusor overactivity due to myelomeningocele. All patients had failed the first-line treatment of a combination of oral antimuscarinics and intermittent catheterization.

Materials and Methods: The study group consisted of 31 children with myelomeningocele with a mean age of 7.95 years (range, 5–13 years) who were followed up for a mean of 29 weeks. The amount of onabotulinum toxin A injected was 10 U/kg with a maximal dose of 300 U. There were 20 to 30 injection sites with rigid cystoscopic guidance under general anesthesia.

Results: Thirty of 31 patients reported dryness between intermittent catheterization intervals. The mean reduction in maximum detrusor pressure and the mean increase in maximum cystometric capacity from baseline were 53% and 51.5%, respectively, 6 weeks after injection. We found a 324% increase in mean bladder compliance and a 57% increase in mean intermittent catheterization volumes. The mean duration of efficacy was 28 weeks with a single injection and 36 weeks for repeated injections (minimum, 16 weeks; maximum, 52 weeks). The mean time interval between repeated onabotulinum toxin-A injections was 7 months (maximum, 13 months). Intradetrusor injections of onabotulinum toxin-A were well tolerated.

Conclusions: Onabotulinum toxin-A injections into the bladder wall provide a significant symptomatic and urodynamic improvement in children with neurogenic detrusor overactivity due to myelomeningocele who are on intermittent catheterization. The treatment seems to be safe and very well tolerated.

Keywords: *Myelodysplastic syndromes; Neurogenic urinary bladder; Onabotulinum toxin-A; Overactive detrusor; Urinary incontinence*

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INTRODUCTION

The most common cause of neurogenic bladder dysfunction in children is the abnormal development of the vertebral canal and the spinal cord. Myelomeningocele (MMC) accounts for more than 90% of all open spinal dystrophic states [1]. Almost all children with MMC have some degree of lower urinary tract functional impairment depending on the level and completeness of the neurological injury [2]. The first line of treatment for achieving low-pressure urine storage and appropriate urine evacuation in children with MMC is a combination of oral antimuscarinics and clean intermittent catheterization (CIC) [3]. Oxybutynin is administered in a dose of 0.2 to 0.4 mg/kg divided two or three times daily. However, this therapy fails in approximately 10% to 15% of patients and can cause severe systemic side

effects such as dry mouth, constipation, and blurred vision, which necessitate discontinuation of the drug even when intravesically administered [4]. If this initial management regimen does not work, alternative methods of treatment should be contemplated.

Augmentation cystoplasty has historically been an effective method for establishing high-capacity, low-pressure reservoir and securing upper-tract drainage, with CIC frequently necessary as an adjunct for achieving optimal urinary continence. However, it remains a major surgical undertaking with significant morbidity. The most common and serious complications are malignancy, bowel obstruction, bladder perforation, urinary tract infections (UTIs), and gastrointestinal dysfunction as well as metabolic disturbances in the long term [5].

The use of onabotulinum toxin-A in the treatment of children with neurogenic detrusor overactivity (NDO) to improve urinary symptoms reduces upper urinary tract (UUT) risk and improves quality of life [6]. This has been developed as a second-line treatment option for children with NDO with urinary incontinence who are able and willing to perform CIC [6].

This study reports our series of treatment with intradetrusor injections of onabotulinum toxin-A in children with MMC and NDO who failed a first-line antimuscarinic and CIC regimen in terms of urinary incontinence.

MATERIALS AND METHODS

Thirty-one children with MMC and urinary incontinence due to NDO who underwent onabotulinum toxin-A intradetrusor injection treatment between August 2006 and December 2012 were enrolled to the study. The study was approved by the Institutional Review Board of Marmara University School of Medicine. The mean age of the group at the time of the injection was 7.95 years (range, 5–13 years). All children had already failed urinary incontinence management with oxybutynin plus CIC for at least 2 months. None of these children had undergone bladder surgery before.

All patients attended the outpatient clinic at regular intervals (about every 6 months) and underwent monitoring that included incontinence score, the bladder diary, urinalysis, urine culture, and renal and bladder ultrasonography. The incontinence score was rated from 0 (completely dry) to 3 (wet >50% of episodes between CICs).

1. Urodynamic evaluation

Urodynamic assessment was conducted simultaneously with the UUT evaluation. Prophylactic antibiotics were given to all patients with vesicoureteral reflux (VUR) or recurrent UTI. Urodynamic studies were conducted in all patients after sterilization of the urine. A computerized urodynamic system was used to evaluate the lower urinary tract. Standard fluid cystometry was done with patients in the supine position by using a 6-Fr double-lumen urethral cystometry catheter and filling at a rate of less than 10% of predicted bladder capacity per minute [30×(age in years×30)] in mL [7].

According to a report from the standardization committee of the International Children's Continence Society, we calculated the maximum detrusor pressure (Pdetmax, cm H_2O), maximum cystometric capacity (MCC), detrusor leak point pressure (cm H_2O), and bladder compliance (mL/cm H_2O) [7].

2. Management protocol

Initial neurourological evaluation was started immediately after the referral from the neurosurgery department and included urine analysis and culture, renal ultrasound, and fluoroscopic urodynamic evaluation. Note that only 15 children in our series received appropriate neurourological management beginning at the newborn period, whereas the remaining 16 children had a delayed primary closure of the spinal defect or neurourological management with CIC and antimuscarinics owing to delay in the referral system. Each child with areflexic detrusor pressures exceeding 40 cm H_2O was started on treatment with oxybutynin (0.2 mg/kg twice daily) and CIC (every 3 hours). For the follow-up, reevaluation with repeated tests was done to confirm the pressure levels every 3 months.

The rest of the urodynamic evaluation was repeated at 12 months and at approximately 36 months of age. Renal ultrasonography provided surveillance for hydronephrosis every 6 months. An increase or new-onset hydronephrosis or febrile UTI prompted an additional voiding cystourethrography and urodynamic evaluation or fluoroscopic urodynamic evaluation [8].

3. Continence

Continence was defined as either at least 4 hours of dryness in CIC intervals or the absence of nighttime or daytime urine leakage in those who gained bladder control.

4. Injection protocol

All patients provided informed consent and were provided detailed information about possible side effects of the treatment option in light of the existing literature. The amount of onabotulinum toxin-A injected was 10 U/kg, with a maximal dose of 300 U under general anesthesia and antibiotic prophylaxis. A single surgeon (T.T.) performed 20 to 30 injections depending on the level of the total dose in the bladder dome and base under rigid cystoscopic guidance with a 3-Fr flexible injection needle. Onabotulinum toxin-A was diluted in 0.9% NaCl so that each injection volume was 1 mL. The base of the bladder was not spared and received 2 to 3 injections, taking care not to inject very close to ureteric orifices. General anesthesia was utilized for all injections.

Repeated injections were recorded for measurement of sustained efficacy both in terms of the urinary incontinence score and urodynamic variables. We also recorded whether these benefits persisted during follow-up periods of 4 weeks, 3 months, and 6 months. We recorded the mean

time interval between repeated onabotulinum toxin-A injections with sustained efficacy both in terms of urinary incontinence score and urodynamic variables.

5. Safety
We analyzed the occurrence of local, systemic, and procedure-related adverse effects.

6. Statistical analysis
The IBM SPSS ver. 20.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. The independent-samples t-test was used to compare the mean scores of data on an interval scale. Fisher exact test was applied to evaluate categorical data and the 2-sided p-value was used in inference. A p-value of <0.05 was considered significant.

RESULTS

1. Study and patient characteristics
Of the 31 children with MMC included in the current study, all had NDO with urinary incontinence despite CIC and antimuscarinic treatment. Follow-up ranged from 12 weeks to 1 year (mean, 29 weeks).

2. Continence
Bladder diaries revealed a 57% increase in the mean CIC volumes in our series (mean preoperative CIC volume, 119.4 mL; mean postoperative CIC volume, 187.2 mL; p=0.0001, t-test). A total of 30 of 31 patients reported continence between CIC intervals.

3. Urodynamic variables
A positive impact of onabotulinum toxin-A treatment on urodynamic variables was demonstrated.

The mean Pdetmax at baseline was 64.63 cm H_2O. The percentage mean reduction in Pdetmax from baseline was 53% in our series (preoperative mean Pdetmax, 64.6 cm H_2O; 6 weeks after injection mean Pdetmax, 30.1 cm H_2O; p=0.01, t-test) (Table 1). The mean MCC at baseline was 153.9 mL. We found the percentage increase in mean MCC from baseline to be 51.5% (preoperative mean MCC, 153.9 mL; postoperative 6 weeks after injection mean MCC, 233.3 mL; p=0.002, t-test) (Table 1). Urodynamic studies revealed a 324% increase in mean bladder compliance in parallel to improvements in MCC and Pdetmax (Table 1).

4. Dynamics of onabotulinum toxin-A treatment
We noticed improvement in terms of continence and urodynamic parameters within 2 to 4 weeks after onabotulinum toxin-A injection. The mean duration of effects was 28 weeks for a single injection and 36 weeks for repeated injections (minimum, 16 weeks; maximum, 52 weeks). Nine patients underwent injections twice and 1 patient underwent triple injections during the follow-up period. There was no extra increase in capacity or compliance with the help of repeated injections compared with the first injection.

TABLE 1. Comparison of Pdetmax, MCC, and bladder compliance before and 6 weeks after injection in the present study and in the literature

First author	No.	Mean baseline			Mean endpoint			Mean change vs. baseline			Mean % change vs. baseline		
		P	MCC	BC	P	MCC	BC	P	MCC	BC	P	MCC	BC
Tarcan	31	64.63	153.9	2.38	30.15	233.3	7.73	−34.48	79.4	5.35	-53	51.5	324
Schulte-Baukloh et al. [9]													
First injection	10	65.7	111.9	11.2	60.7	231.3	15.4	−5.0	119.3	4.2	−8	107	38
Third injection	10	73.6	214.6	9.1	41.8	220.8	16.3	−31.8	6.2	7.2	−43	3	79
First injection	4[c]	52.0	160.3	21.7	48.3	301.0	21.7	−3.7	140.7	0.0	−7	88	0
Fifth injection	4	58.5	235.3	10.3	36.0	403.7	21.5	−22.8	168.4	11.2	−39	72	109
Schulte-Baukloh et al. [10]													
Week 4	14	59.6	163.1	15.8	34.9	219.9	50.9	−24.7*	56.8*	35.1*	−41	35	222
Week 12	15	59.6	163.1	15.8	46.7	200.6	24.9	−12.9	37.5*	9.1	−22	23	58
Week 24	8	59.6	163.1	15.8	61.8	222.4	14.1	2.2	59.3*	−1.7	4	36	−11
Riccabona et al. [11]													
Week 12	15[d]	78.8	136.3	18.3	42.8	297.0	51.2	36.0[e,**]	160.7[e,**]	32.9[e,**]	−46	118	180
Week 36	15[d]	78.8	136.3	18.3	48.3	284.0	48.0	30.5[e,**]	147.7[e,**]	29.7[e,**]	−39	108	162
Week 48	15[d]	78.8	136.3	18.3	77.7	154.0	20.2	−1.1[e]	17.7[e]	1.9[e]	−1	13	10
Schulte-Baukloh et al. [12]	17	58.9	137.5	20.4	39.7	215.3	45.2	−19.2*	77.8*	24.8*	−33	57	122
Altaweel et al. [13]	20	43.0[a]	215.6[a]	5.2[a]	21.6[a]	338.3[a]	13.0[a]	−21.4[b,*]	122.7[b,*]	7.8[b,*]	−50	57	150

P, Pdetmax (cm H_2O); MCC, maximum cystometric capacity (mL); BC, bladder compliance (mL/cm H_2O).
[a]:Results for 13 continent patients. [b]:Similar improvement after second injection. [c]:Same patients who received fifth injection. [d]:All patients received a second injection after 1 year. [e]:Similar improvement after second injection.
*$p<0.01$. **$p<0.001$.

5. Upper urinary tract

Preoperatively, VUR was observed in 14 renal units (RUs) of 11 children. Reflux grade was grade III or higher in 8 RUs and scarring was observed in 9 RUs by dimercaptosuccinic acid scintigraphy. Reflux disappeared on 5 RUs and grades decreased on 5 of 14 RUs. Grades of VUR were the same on 2 RUs and upgraded on 2 RUs (1 patient). Hydronephrosis disappeared postoperatively on 4 RUs and decreased on 5 RUs. Onabotulinum toxin-A injection led to a resolution of VUR in 35% of RUs and to a downgrade in another 35% of RUs in children with detrusor overactivity. Particularly, 1 patient with upgraded bilateral VUR showed no improvement in urodynamic parameters.

6. Safety

Onabotulinum toxin-A intradetrusor injections were well tolerated in our study population. The most frequent adverse effects appeared to be procedure-related UTI. As shown in Table 2, 9 of 31 patients in our study group reported symptomatic UTI after injection. Skeletal muscle weakness was not reported to have occurred in our study.

DISCUSSION

As the results of the current study and previously published studies have shown, the injection of onabotulinum toxin-A into the detrusor of children with NDO and related urinary incontinence, who have failed antimuscarinic therapy, has beneficial effects on both clinical and urodynamic variables [9-13]. However, on the basis of the currently available data and physicians' experience, the best application and methodology of onabotulinum toxin-A injection in children is still under debate. In our opinion, patients with symptoms related to NDO who have failed antimuscarinic therapy and who are willing and able to perform CIC seem to be best candidates for onabotulinum toxin-A treatment.

The current onabotulinum toxin-A injection treatment protocol was almost the same as in previous studies with respect to patient characteristics, amount of onabotulinum

TABLE 2. Detailed analysis of the study group

Patient's no.	Baseline	Endpoint	Baseline	Endpoint	Side effects	No. of Botox	On CIC before treatment
	P	P	MCC	MCC			
1	38	20	109	400	0	2	Yes
2	29	25	78	235	1	2	Yes
3	123	41	82	122	0	1	Yes
4	108	40	217	400	0	1	Yes
5	26	29	324	600	1	1	Yes
6	28	15	122	220	1	1	Yes
7	65	30	55	150	0	1	Yes
8	67	37	159	250	0	1	Yes
9	55	27	271	180	0	2	Yes
10	56	38	71	122	0	1	Yes
11	81	14	94	174	0	1	Yes
12	39	21	57	143	1	1	Yes
13	325	40	180	89	1	3	Yes
14	84	41	180	230	1	1	Yes
15	37	11	45	191	0	2	Yes
16	29	18	250	320	0	1	Yes
17	86	61	99	88	0	2	Yes
18	31	20	195	280	0	1	Yes
19	53	53	19	107	0	1	Yes
20	21	14	125	196	0	1	Yes
21	43	35	157	261	0	1	Yes
22	93	46	123	212	1	2	Yes
23	44	34	385	369	0	1	Yes
24	28	16	204	271	1	1	Yes
25	41	23	80	125	0	2	Yes
26	64	32	98	198	1	1	Yes
27	26	14	197	240	0	2	Yes
28	28	12	204	254	0	1	Yes
29	70	44	260	355	0	2	Yes
30	90	37	120	210	0	1	Yes
31	95	46	130	240	0	1	Yes

P, Pdetmax (cm H_2O); MCC, maximum cystometric capacity (mL); CIC, clean intermittent catheterization; 0, no side effects; 1, urinary tract infection after procedure.

toxin-A, dilution method, injection sites, and number of injections compared with previous studies [9-13]. The most common minimal age required to propose intradetrusor injection of onabotulinum toxin-A was 2 years in previous studies, but we prefer a minimum age of 5 years for this group of patients because the limit corresponds to the age approved by legal authorities like the U.S. Food and Drug Administration and European Medicine Agency. In our opinion, vesicostomy is a good option in toddlers with NDO that is resistant to medical treatment to prevent UUT deterioration. The most commonly used dose of onabotulinum toxin-A is 10 U/kg, with a maximal dose of 300 U (Table 2). Unfortunately, no dose-study has been performed in children; thus, no conclusions could be reached regarding the optimal dose. However, recent studies have shown that in adults with NDO, 200 U of onabotulinum toxin-A results in the same efficacy as the dose of 300 U [14,15]. Therefore, we have currently decreased the dose of onabotulinum toxin-A in children to 5 U/kg with a maximum dose of 200 U. Usually, 20 to 30 injections of 10 U/kg/mL were performed. Hence, the long-term risk of fibrosis could potentially be reduced and injections consequently be made less painful, therefore allowing local anesthesia, especially in adolescent patients. In all studies, injections have been performed directly into the detrusor by using a rigid cystoscope and under general anesthesia. However, some authors believe that local anesthesia may be proposed for neurogenic patients who are at risk of autonomic dysreflexia. We preferred rigid cystoscopy under general anesthesia and did not report any side effects related to the procedure or the anesthesia.

Our experiences revealed that onabotulinum toxin-A has a fast onset of action with significant effects reached within 2 weeks and maximum effects within 4 to 6 weeks. The longer term repeated injections study suggests that the effect of an intradetrusor injection of onabotulinum toxin-A lasts for 34 weeks, or approximately 7 to 8 months [12,13]. Because the shorter-term studies suggest that the duration of action was shorter than reported, the duration of effect should therefore be further clarified in specifically designed studies.

For the vast majority of studies, the antimuscarinic regimen used throughout the study was not clearly described and therefore its potential impact on the efficacy of onabotulinum toxin-A cannot be assessed. Although Neel reported that oxybutynin had no augmentative effect on onabotulinum toxin-A, we continued the antimuscarinic regimen with CIC during follow-up of patients owing to a lack of well-designed studies [16].

As shown in Table 1, mean Pdetmax was reduced to at least 40 cm H_2O and bladder compliance increased to at least 20 cm H_2O. The reduction in Pdetmax was accompanied by an increase in MCC. However, these results are limited by a lack of controlled studies and the fact that most of the studies involved less than 20 patients, except that by Kajbafzadeh [17]. In our studies, the improvement of compliance was higher than in the other series (Table 1). This may be the result of the lower baseline compliance values compared with other studies.

Most articles have reported adverse effects, and procedure-related UTIs are the common adverse effects measured [18,19]. Although in the current study 9 of 31 (29%) patients reported symptomatic UTI, we could not differentiate the main reason for infection as a CIC-related UTI. Skeletal muscle weakness was never reported in children after onabotulinum toxin-A intradetrusor injections. The proper dose selection has to be further explored in specifically designed studies. Moreover, no studies in children have assessed the impact of repeated injections on the bladder wall, the risk of fibrosis, or alterations in bladder compliance over time. These impacts have to be further clarified in specifically designed studies.

We prefer reinjection after a predefined time interval of 7 to 8 months on the basis of literature data on the duration of effect and reinjection according to symptoms or urodynamic worsening. We believe that patients should not receive repeated injections in cases of remaining compliance problems or because of limited or no urodynamic or symptomatic improvement after 2 to 3 injection sessions. These patients should seek other treatment alternatives.

In the present study, we injected into the trigone (2 or 3 injections) but spared the ureteral orifices. We found a resolution of VUR in 35% of RUs and a downgrade in another 35% of RUs in our series. Upgraded bilateral VUR was observed in 1 patient whose urodynamic parameters did not improve after injection. Most of the clinical trials published to date have spared the trigone in order to avoid potential VUR, although there is no clinical evidence to recommend trigone sparing. In contrary, the trigone is very densely innervated and likely has a role in initiating involuntary contractions. In a recent prospective, single-blind, parallel, controlled clinical study, two study arms, each with 18 spinal cord–injured patients with NDO, were compared [20]. In the detrusor arm, 300 units of botulinum toxin-A was injected in the detrusor muscle, sparing the trigone. In the combined arm, 200 units were injected in the detrusor muscle and 100 in the trigone. The authors found that at week 8, incontinence decreased by 52.4% vs. 80.9% and complete dryness was achieved in 33.3% vs. 66.7% of patients in the detrusor and combined arms (p=0.001), respectively. The absolute difference was 60% vs. 82.5% for reflex volume (p=0.001). At week 18, anticholinergics were needed again in 50% and 22.2% of patients, respectively. No patient showed new or upgraded VUR [20]. In another prospective randomized controlled trial comparing trigone-sparing versus trigone-including intradetrusor injection of 500 U AbobotulinumtoxinA for refractory idiopathic detrusor overactivity, the mean total overactive bladder symptom score and the urgency subscale scores at 6, 12, and 26 weeks improved significantly in favor of the trigone-including group, and no patients developed VUR [21]. These latter 2 studies on adult populations have indicated that trigone-including injections are superior to trigone-sparing injections for the treatment of neurogenic

and idiopathic refractory detrusor overactivity and do not cause VUR. Our study provides only a level 3 of evidence for the safety and efficacy of trigone-including injections in children with NDO. Therefore, randomized controlled studies are certainly needed in children to generate a higher level of evidence.

CONCLUSIONS

In children with NDO-induced urinary incontinence refractory to antimuscarinics, intradetrusor injections of onabotulinum toxin-A should be the second-line treatment of choice, thus decreasing the need for augmentation cystoplasty. Changes to the UUT should be carefully assessed during follow-up after injection, because improved urinary continence does not necessarily ensure the safety of the upper system. Intradetrusor onabotulinum toxin-A seems to be very well tolerated with minimal local and systemic side effects. However, randomized controlled trials are necessary to confirm efficacy and safety, assess optimal injection sites, and assess the optimal dose with the longest duration of efficacy.

This study reports our series of onabotulinum toxin-A intradetrusor injections without placebo control. All of the patients were under CIC. The antimuscarinic regimen was continued throughout the study and therefore its potential impact on the efficacy of onabotulinum toxin-A cannot be assessed. The dose of 10 U/kg with a maximum of 300 U used in the present study is similar to previous studies in the literature; however, recent data suggest that a lower dose of onabotulinum toxin-A may be as efficacious as the conventional high dose. The optimal dose in children needs to be assessed by further studies. We did not have enough patients to discuss the repeated doses outcome. We did not sample bladder tissue to clarify the fibrosis issue in this treatment option. We did not use a flexible cystocope, so we cannot report the office usage of this treatment option under local anesthesia.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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