Evaluation of the Clinical Effects of Abobotolinum Toxin A (Dysport) Injection in the Treatment of Neurogenic Lower Urinary Tract Dysfunction

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Purpose: Neurogenic lower urinary tract dysfunction (NLUTD) is one of the most challenging problems in urology. In recent years, Onabotulinum toxin A (Botox) is considered a second-line treatment in these patients. This study aimed to evaluate the clinical effects of Abobotolinum toxin A (Dysport) into the bladder and urethra.

Materials and Methods: We classified our patients with NLUTD into three groups: neurogenic detrusor overactivity (group 1), detrusor sphincter dyssynergia (group 2), and patients with both symptoms (group 3). The severity of the patient's symptoms was assessed using the Urinary Distress Inventory- Short form (UDI-6), urodynamic study, and post-void residual urine (PVR) at baseline. After injection of Dysport, the patients were evaluated by the change in UDI-6 score, PVR, and the patient's general satisfaction. In group 1, 500-900 U diluted Dysport injected intra-vesical. If associated with detrusor sphincter dyssynergia (group 3), 100 U diluted Dysport injected peri-urethral. In group 2, only 100 U diluted Dysport injected peri-urethral.

Results: Data from 52 women with NLUTD were analyzed. The mean age was 51.3 ± 21.6 years. The prevalence of detrusor overactivity and the value of Q max was more in group 1. However, the amount of PVR was more in groups 2 and 3. The overall success rate was acceptable in all three groups. In addition, there were significant improvements in UDI-6 parameters.

Conclusion: Peri-urethral injection of Abobotolinum toxin A is effective and safe. However, the selection of the patients and the dose of toxin needs more studies.

Keywords: Abobotolinum toxin A; neurogenic; urethra; voiding dysfunction

INTRODUCTION

Appropriate diagnosis and management of patients with neurogenic lower urinary tract dysfunction (NLUTD) are among the most challenging problems in urology through significant medical and social aspects. Various disorders or injuries of the central or peripheral nervous system (i.e., stroke, spinal cord injury, Parkinson's disease, multiple sclerosis, etc.) may cause NLUTD. These events' consequences depend on the location and extent of the neurologic lesion leading to neurogenic dysfunction of the urinary bladder with or without adverse effects on the urethra[1]. Neurogenic detrusor overactivity (NDO), detrusor sphincter dyssynergia (DSD), incomplete voiding and high pressure often lead to structural bladder damage, upper urinary tract dilation, vesicoureteral reflux, and renal insufficiency. Therefore, the main goals of NLUTD treatment consist of preserving renal function, achieving urinary continence, prevention and control of urinary tract infection, with improved quality of life[1].

The current methods to manage NLUTD include medications, botulinum toxin A (BTX-A) injection, neuromodulation, and surgical procedures. Each of these has advantages and disadvantages[2]. Nowadays, the combination of anticholinergic drugs with clean contamination catheterization (CIC) is the gold standard treatment for NDO[2]. Onabotulinumtoxin A (Botox) has been approved to treat NDO in certain parts of the world, such as the USA[3], on the theoretical basis that injection into the detrusor muscle would temporarily block the presynaptic release of acetylcholine from parasympathetic innervation. Therefore, Botox injection can result in the paralysis of the detrusor smooth muscle that may last for an estimated nine months[2].

One of the common problems in patients with NLUTD is detrusor sphincter dyssynergia, which increases the post-void residual urine (PVR)[4] and results in urinary tract infection or upper urinary tract deterioration. Urethral injections of Botox were proposed by Dykstra et al. in 1988[5]. Steinhardt et al. were the first to report Botox's injections into the urethral sphincter of children with neurogenic voiding dysfunction in 1997[6]. After that, Botox injection in the urethral sphincter has become popular in various neurogenic or non-neurogenic

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Table 1. Determination and comparison of demographic variables in the two groups.

	NDO (n=36)	DSD (n=8)	NDO with DSD (n=8)	*p*-value
Age: mean± SD	48 ± 20	57 ± 27	49 ± 18	0.583[a]
BMI: mean± SD	26.52 ± 5.16	29.35 ± 8.11	30.10 ± 5.31	0.181[a]
UDS				
DO: n (%)	22 (61.1)	1 (12.5)	6 (75.0)	0.028[b]
Capacity: mean± SD	288 ± 115	408 ± 230	330 ± 91	0.153[a]
Q max: median (IQR)	13 (10.4-15)	8.3 (6.5-15)	8 (5-8)	0.004[c]
PVR: median (IQR)	15 (9.5-37.5)	100 (20-200)	80 (24-237)	0.053[c]

*Significant at level of 0.05, a. ANOVA, b, Fischer exact test, c. Kruskal-Wallis test
Abbreviations: NDO. Neurogenic detrusor overactivity, DSD. Detrusor sphincter dyssynergia, BMI. Body mass index, UDS. Urodynamic study, DO. Detrusor overactivity, PVR. Post void residual urine, SD. Standard deviation, IQR. Interquartile range.

conditions, including voiding dysfunction, detrusor underactivity, or chronic urinary retention[7]. According to the literature, this treatment's effectiveness is reported in 60–100% of patients with spinal cord injury, which can last up to six months without significant side effects (8). However, dosage, injection schedule, and period of efficacy vary from article to article[9].
Most of the existing studies have focused on injecting Onabotulinum toxin A (Botox) in patients with NLUTD. In this study, we evaluate the clinical efficacy of Abobotolinum toxin A (Dysport) injection into the bladder, peri-urethra, or both. Abobotolinum toxin A (Dysport) is the only commercially available BTX-A in our country, which there is very little evidence in this regard in the literature till now.

MATERIALS AND METHODS

Study population

In this prospective study, patients with symptoms of NLUTD who were referred to a tertiary urology clinic were recruited during 2018- 2019, based on convenience sampling. The patient's symptoms including urgency, frequency, urinary incontinence (urge or stress), incomplete voiding, and pain or discomfort during voiding. All patients were female, ≥18 years old with refractory to medical treatment (for at least three months), and no BTX-A injection history. In those with active or recurrent urinary tract infection (UTI), prompt medical therapy was prescribed, and in persistent UTIs, effective suppressive antibiotic treatment was registered. The exclusion criteria were the inability to complete the questionnaire, significant stress incontinence, interstitial cystitis, bladder carcinoma, urinary tract stones, intolerance or inability to perform clean self-intermittent catheterization, and pregnancy or lactation. In addition, we excluded any patients with moderate to high hydroureteronephrosis or serum creatinine ≥1.5 mg/dl.
The patient's symptoms were assessed by validated Urinary Distress Inventory- Short form (UDI-6)[10], urodynamic study (UDS), and the amount of PVR at baseline. The patient's outcome was assessed by change in the UDI score, the amount of PVR, and patients' general satisfaction.[11] UDI-6 questionnaire is defined by six items with a total score ranging from 0 to 18, with higher scores indicating increasing symptom severity[10]. The UDS parameters including; detrusor overactivity (DO), defined by involuntary detrusor contractions during the filling phase and, DSD, defined as a detrusor contraction concurrent with an involuntary contraction of the urethral or periurethral striated muscles[12]. The patients' general satisfaction was evaluated by the summation of improvement in urinary incontinence, difficult urination, and the need for CIC. After treatment, the patient's satisfaction scored 0–3, representing not, mild, moderate, and very satisfied. The final therapeutic result was categorized as a successful outcome, including moderate, and very satisfied and failed outcomes representing those without or low satisfaction.
Written informed consent was obtained from all patients before enrollment in the study. The ethics committee of the Urology Nephrology Research Center of Shahid Beheshti University of Medical Sciences approved this study (ethic code: IR. SBMU.UNRC.1397.16). Also, this is under the Helsinki declaration of 1964 and its later amendments. Patients were informed about the study objectives in their language.

Procedure

All patients were assessed at baseline by routine history, physical examination, urine analysis, urine culture, and urinary tract ultrasound (to measure PVR). The patients were also assessed by the UDI-6 questionnaire and urodynamic examination.
Before cysto-urethroscopy, 500-900 U Abobotolinum toxin A (Dysport, 500 U/vial, ISPEN, UK) was diluted in 6 ml of saline 0.9%. The amount of required Dysport was calculated according to the patient's weight, ten units per kilogram. In patients with NDO, diluted Dysport was injected intra-vesical by a 27-G disposable needle into 30 sites in the bladder wall to distribute drugs better. If associated DSD, 100 U Dysport (equal to 35 U of Botox) was injected peri-urethral, at 3, 9, and 12 O'clock in presumed external urethral sphincter place. In patients who only had DSD symptoms, such as an intermittent urinary stream or low maximal flow rate, 100 U of Dysport diluted in 1 cc normal saline injected peri-urethral using 31-gauge insulin syringe (**Figure 1**). After the procedure, a 14 Fr. Foley catheter was placed and removed the next day, routinely. Broad-spectrum antibiotics were given for 3 to 5 days after injection. At discharge note, patients were advised to come to the emergency department for any acute problems.
Patients visited one month then followed four months after the procedure in the outpatient clinic. During this time, anticholinergic drugs were discontinued after Dysport injection.

Statistical analysis

For data analysis, the first normal distribution of data was evaluated by the Shapiro-Wilks test. Mean, standard deviation (SD), median, interquartile range (IQR), frequency, and percent were reported to describe variables. A Fischer exact test was used to explore the association between categorical variables. ANOVA (or Kruskal-Wallis test) and paired t-test (or Wilcoxon test)

Table 2. The overall success rate of the three groups of patients according to the general patient's satisfaction after four months of Abobotolinum toxin A (Dysport) injection.

	Failed	Success
NDO: n (%)	12 (38.7%)	19 (61.3%)
DSD: n (%)	2 (28.6%	5 (71.4%)
NDO with DSD: n (%)	0 (28.6%)	6 (100.0%)
Total: n (%)	14 (28.6%)	30 (68.2%)

Abbreviations: NDO. Neurogenic detrusor overactivity, DSD. Detrusor sphincter dyssynergia.

were used for between and within-group comparisons in terms of numeric variables. $P < 0.05$ is considered significant. Statistical analysis was done using SPSS (statistical product and service solution) 21.

RESULTS

Fifty-two consecutive adult women with symptoms of NLUTD were included. The mean age was 51.3 ± 21.6 years. Table 1 shows the characteristics of three groups of patients with NLUTD; group 1: neurogenic detrusor overactivity (NDO), group 2: patients with detrusor sphincter dyssynergia (DSD), and group 3: patients with NDO accompanied with DSD. Regarding comorbid diseases, four patients had a history of diabetes, 13 patients had high blood pressure and, the cause of NLUTD in 17 patients was spinal canal diseases (Intervertebral disc prolapse, trauma, or after disc surgery). The prevalence of detrusor overactivity and higher Q max was more in group 1 of patients, as the PVR amount was lower than the other two groups (**Table 1**).

Peri-operatively, there were no acute complications during the injection. Post-injection adverse events, including hematuria, were found in 11 patients (21.15%), urinary tract infection in 8 patients (15.38%), and fever in 3 patients (5.76%) who responded to outpatient medical treatment.

Four months after Dysport injection, the overall success rate in valid cases was 61.3% in group 1, 71.4% in group 2, and all of the patients in group 3 (according to the general patient's satisfaction). There is no significant difference in success rate between the three groups of patients (Table 2). Table 3 shows the changes in UDI-6 scores (each question) at baseline and four months after Dysport injection in patient groups. Significant improvements in frequency (Question 1) and difficult voiding (Question 5) were observed in all patients. However, PVR significantly decreased in group 2 (DSD), and group 3 (NDO associated with DSD).

DISCUSSION

Onabotulinumtoxin A (Botox) has been approved to treat neurogenic detrusor overactivity in certain parts of the world, such as the US and the UK[3]. Herein; we present our experience of Abobotolinum toxin A (Dysport) injection in patients with NLUTD. There was a significant improvement in urinary symptoms and general patient satisfaction in three groups of our patients with NDO, DSD, and NDO with DSD. Post void residual urine was significantly decreased in patients with DSD as NDO associated with DSD.

BTX-A is a potent neurotoxin, which can inhibit the release of neurotransmitters from efferent nerve terminals at neuromuscular junctions, thereby paralyzing the muscle[13]. Therefore, the use of Botox in the bladder detrusor muscle and urethral muscles has been considered for many years. However, since central and peripheral nerve pathways are related to the bladder and urethra's function, injection of BTX-A in one of them will affect another.

According to the literature, when the bladder is filled, stimulation of some afferent nerves in the bladder influences external urethral sphincter activity by central neural mechanisms such as guarding reflex[14,15]. In addition, Shafik et al.[16] described that during bladder filling, when the vesical pressure increases, the pressure in the internal urethral meatus (urethral smooth muscle) rises. Based on the literature referenced above, detrusor relaxation by BTX-A injections in the bladder muscle induces fewer triggering of the mechanoreceptors in the

Table 3. Comparing the UDI-6 score and post-void residual urine in three groups of patients with neurogenic lower urinary tract dysfunction at baseline and four months after Abobotolinum toxin A (Dysport) injection.

UDI-6	NDO Median (IQR)	DSD Median (IQR)	NDO with DSD Median (IQR)
Question 1: BL	3 (3-3)	3 (3-3)	3 (3-3)
Question 1: 4M	1 (1-3)	1 (1-3)	1 (1-1)
p-value[b]	<.001	.034 *	.008 *
Question 2: BL	3 (3-3)	1 (0-3)	2 (1-3)
Question 2: 4M	0 (0-1)	1 (1-2)	1 (1-2)
p-value[b]	<.001	.157	.038 *
Question 3: BL	1 (0-3)	1 (0-2)	1 (0-2)
Question 3: 4M	0 (0-2)	1 (0-2)	0 (0-1)
p-value[b]	.010 *	0.998	.180
Question 4: BL	3 (2-3)	2 (1-3)	2 (1-3)
Question 4: 4M	1 (0-3)	0 (0-2)	2 (1-3)
p-value[b]	<.001	.028 *	0.998
Question 5: BL	0 (0-1)	3 (3-3)	3 (2-3)
Question 5: 4M	0 (0-1)	1 (1-2)	1 (1-2)
p-value[b]	.046 *	.024 *	.034 *
Question 6: BL	1 (0-3)	3 (3-3)	2 (1-3)
Question 6: 4M	0 (0-2)	0 (0-2)	2 (1-3)
p-value b	.038 *	.018 *	0.998
PVR-BL	22.50 (10.00-50.00)	120.00 (50.00-350)	140.00 (39.00-225.50)
PVR-4M	25.00 (15.00-45.00)	55.00 (32.50-150.00)	65.00 (15.00-125.00)
p-value [b]	.104	.027	.017

a.Kruskal-Wallis, b. Wilcoxon

Abbreviations: UDI-6. Urinary Distress Inventory- Short form, NDO. Neurogenic detrusor overactivity, DSD. Detrusor sphincter dyssynergia, PVR. Post void residual urine, BL. Baseline, 4M. Four months after injection.

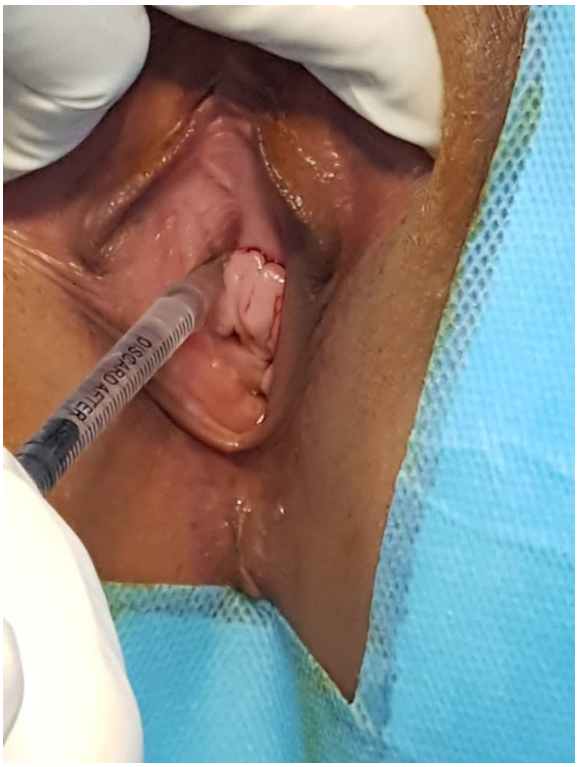

Figure 1. Injection of diluted Dysport in peri-urethra at 12 o'clock using 31-gauge insulin syringe.

bladder wall and consequently a decrease in urethral pressure[9]. Therefore, the use of intravesical BTX-A in NDO could improve bladder outlet obstruction; since the patient experienced easier CIC.

On the other hand, urinary bladder emptying requires the relaxation of the bladder neck and urethral sphincter followed by the contraction of detrusor smooth muscles, and voluntary coordinated urethral sphincter relaxation completes the voiding process[17]. Coordination between the urethral sphincter and the urinary bladder is mediated by complex neural control and reflex pathways. So, during the voiding phase, when the urethral sphincter is poorly relaxed, a forceful detrusor contraction may be inhibited by inhibiting the detrusor contraction micturition center at the sacral spinal cord[18]. Whenever the urethral sphincter contraction during the voiding phase can also inhibit detrusor muscle contraction by activating the inhibiting afferent reflex[14]. Therefore, both a poorly relaxed urethral sphincter and a urethral sphincter with contraction during voiding not only interfere with urinary flow, causing a functional bladder outlet obstruction but also affect the detrusor contractions contributing to bladder dysfunctions, such as detrusor underactivity. Conceptually, urethral sphincter injection with BTX-A might facilitate voiding by reducing urethral resistance due to its paralyzing effect and enhancing detrusor contraction due to its potential neuromodulation effects[7].

Another mechanism that can explain BTX-A injection on the neighboring structure might be the spread of toxins in contiguous structures. It means that besides the effect on bladder function, BTX-A may affect the bladder neck. Caremel et al. have discussed this idea of dispersion of detrusor-injected toxin towards the internal sphincter[19]. In this retrospective study of 11 patients with spinal cord injury and repeated Botox treatment, Caremel et al. found a decreased ejaculated volume in 10 patients following Botox treatment compared to pretreatment patients, concerning the increased incidence of retrograde ejaculation. With the same idea of passive distribution, some others described that fewer injection sites of toxin in detrusor were as useful as the established technique with more injection areas[20]. Despite the limited injection sites, it implies migration of BTX-A throughout the whole detrusor, meaning a local and systemic diffusion[9].

Although BTX-A injections into the bladder and urethra have been widely used in recent years, various studies have different success rates. The possible reasons for this discrepancy or failure of some studies are not fully understood. The difference in success rate is the dose and site of injection (bladder or urethra or both). In a study involving patients with low detrusor contractility, 48% (13 of 27) of patients who received an injection of 50–100 U Botox into the urethral sphincter showed improvement in detrusor contractility, indicating the neuromodulation effects between the urethral sphincter and bladder[21]. Another study by Kuo et al. revealed that in patients with DSD, urethral sphincter injection of 100 U Botox reported to achieve an overall satisfactory result of 60.6% with significant improvement in the reduction of voiding detrusor pressure and post-void residual urine volume and an increase in maximal urinary flow rate[22]. They showed that in spinal cord injured patients with DSD, de novo urge urinary incontinency (48.5%) was the main reason for patient dissatisfaction with urethral sphincter Botox injection therapy[22]. In adult patients, Liao et al. reported that urethral sphincter injection with a usual dose of 50–100 U Botox resulted in an overall success rate of 86.7% in patients with dysfunctional voiding and a success rate of 95.7% in patients with poor relaxation of the urethral sphincter[23]. Franco et al. reported that increasing the Botox dose to 200–300 U resulted in increased efficacy without increasing the morbidity rate[24]. Botox's repeated injection in urethral sphincter with better therapeutic effects in both dysfunctional voiding and detrusor underactivity patients, indicating that a higher dose or repeated injection of Botox is necessary for optimal pharmacologic effects in these patients.

Other reasons for the differences in the success rate of BTX-A injection in patients with NLUTD are the type and brand of toxin[25] and associated pathology such as detrusor underactivity or bladder neck dyssynergia[26]. For example, in patients with detrusor underactivity, urethral sphincter Botox injection might result in a reduction in urethral resistance, which allowed patients to void more easily with the aid of abdominal pressure. However, if the patient is weak and cannot generate adequate abdominal pressure to void, voiding difficulty and large post-void residual volume might persist. Also, an open bladder neck is essential because abdominal pressure can passively overcome the urethral resistance. If patients with detrusor underactivity cannot open the bladder neck by abdominal straining, urethral sphincter Botox injection might not be successful[7].

A stricter definition of successful results in some studies is also mentioned. Psychogenic factors can also affect sphincter relaxation. In a randomized, double-blind, placebo-controlled trial study by Jiang et al.,

comparing the efficacy of Botox with placebo (normal saline) injections into the urethral sphincter in patients with dysfunctional voiding and detrusor underactivity had been shown. Interestingly, the therapeutic effects of the placebo were similar to those of Botox subgroups. It seems that the local injection of either substance into the urethral sphincter might result in reduced spasticity of the urethral sphincter in patients with dysfunctional voiding. Stimulation of the urethral sphincter via solution injection might provide partial urethrolytic effects on a spastic, poorly relaxed, and non-relaxed urethral sphincter, ameliorating voiding symptoms and facilitating bladder emptying that increased relaxation of the urethral sphincter in patients with detrusor underactivity, regardless of the pharmacologic effects of BTX-A. However, only toxin injection in the urethra resulted in increased maximum flow rate and voided volume, and reduced detrusor pressure, which demonstrates the paralytic effect of BTX-A[7].

Our study's primary limitations are the small number of patients with a lack of control groups. Also, the heterogeneous underlying pathogenesis of our patients with NLUTD. The third limitation was the relatively short follow-up period. A longer follow-up might reveal better pharmacologic effects of BTX-A on the urethral sphincter and eliminate the placebo effects.

CONCLUSIONS

According to our findings and previous studies, the periurethral injection of BTX-A (Botox or Dysport) is effective and safe in decreasing urethral resistance in DSD besides the routine use of Botox in patients with NDO. Therefore, the urethra is a potential therapeutic target in patients with NLUTD. However, dosage, injection schedule, and patient selection should be standardized to facilitate bladder emptying, improve subjective symptoms, and life quality. Our findings can help clinicians choose an alternative treatment in some patients, especially those unwilling or unable to perform clean intermittent catheterization.

CONFLICT ON INTEREST

The authors have no conflicts of interest to declare.

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