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The effects of botulinum toxin injection on urodynamic changes in pediatric population with neurospastic bladder: First trial in Iran☆

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ABSTRACT

Background: Neurogenic bladder is one of the serious, disturbing problems referred to pediatric urologic clinics. The increase in bladder pressure may damage the upper urinary tract. Anticholinergic medications have been used as the first line of complementary treatment. Regardless can be omitted, botulinum toxin (BT) was introduced as an alternative method for increasing bladder compliance. BT is a neurotoxic poison that can interfere with acetylcholine release, leading to reduced external sphincter pressure and detrusor activity. This study was established to assess urodynamic changes following BT injection among Iranian pediatric population, for the first time.

Methods: This clinical trial was conducted at Shahid Beheshti University of Medical Sciences (SBUM), Tehran, Iran, from November 2018 to January 2019 as a medical graduation dissertation. Twenty patients, previously as followings with a neurogenic bladder who met the eligibility criteria, underwent BT injection with general anesthesia using a rigid cystoscope and an endoscopic needle. Demographic data, history of anticholinergic consumption, side effects or intolerance, and the dosage of the injected BT were all recorded. The urodynamic variables during our study included: flow rate in second two, the flow time of diuresis, time of peak flow, average flow, discharged volume, maximum detrusor muscle filling pressure, maximum flow, acceleration, post-void residual volume, compliance, and cystometric bladder capacity. SPSS software version 22 was used to analyze data. The significance level was considered less than 0.05.

Results: Twenty patients who did not respond to anticholinergic medications or could not tolerate the side effects were entered the study. The mean age was 7.7 ± 2.02 years (range 5–13), and 13 (65%) of them were male. All patients received anticholinergic medications before BT injection. Discharge volume and maximum detrusor muscle filling pressure showed the most significant changes after injection ($p < 0.005$). However, there was no significant effect of the baseline characteristics on post-injection improvement in urodynamic results ($p > 0.05$).

Conclusion: In this study, maximum detrusor filling pressure and discharge volume were both significantly improved. These findings motivate additional studies towards selecting better indexes for defining the clinical improvement and its relation with specific urodynamic results.

Level of Evidence: Treatment study, level III.

Neurogenic bladder is one of the common disturbing problems referred to pediatric urology clinics. The consequent increase in bladder pressure may damage the upper urinary tract (UUT). Urinary incontinence is one of the main consequences of the neurogenic bladder that impairs the quality of life [1]. Anticholinergic medications have been used as the first line of complementary treatment in patients who undergo classic intermittent urinary catheterization [2]. Medication side effects or failure in achieving the desired response with a maximum tolerable dosage of the drug, have caused the withdrawal of treatment in some patients. Anticholinergic side effects consist of dry mouth, flushing, constipation, and behavioral changes [3]. Thus, the ultimate goal of treating neurogenic bladder is to reduce the risk of UUT damage, infection, and incontinence.

Botulinum toxin (BT) has been introduced as an alternative method for increasing bladder compliance by reducing external sphincter

Abbreviations: BT, Botulinum toxin; ICCS, International Children Continence Society; IRCT, Iranian Registry of Clinical Trials; SBUM, Shahid Beheshti University of Medical Sciences; UTI, Urinary tract infection; UUT, Upper urinary tract; VCUG, Voiding cystourethrography.

☆ **Trial Registration:** The trial was enrolled in Iranian Registry of Clinical Trials (IRCT) and encoded IRCT20181124041743N1.

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pressure and detrusor activity [4]. One of the first works in 2003 [5] about the effect of BT on the spastic bladder, revealed significant changes in reflex volume, maximal detrusor pressure, bladder capacity, and compliance after 3 months.

BT produced by Clostridium botulinum bacteria is a neurotoxic poison that can interfere with acetylcholine effect by decreasing its release in nerve endings [6, 7]. Of eight subtypes of exotoxins, type A has been used for correcting strabismus [8] first in 1981 and then for neuropathic pain syndrome, dystonic spasms, and urethral dysfunction following spinal cord damage via injection to the perineum or cystoscope [9]. BT opened a new window to successful improvement in patients who suffered from lower urethral tract disease, especially those with spastic muscular changes and resistant to medication therapy [10].

This study was established to assess urodynamic changes following BT injection among Iranian pediatric population, for the first time. Further, some urodynamic evaluations investigated by our group have not been considered in previous studies and may bring some new hypothesis regarding this alternative approach in children with neuropathic bladder.

1. Methods

1.1. Design and materials

The current research was conducted at Shahid Beheshti University of Medical Sciences (SBUM) from November 2018 to January 2019 as a medical graduation dissertation. All patients, previously diagnosed with neurogenic bladder, referred to our clinic, were considered for further evaluation if they met the inclusion criteria of the study. Patients that needed BT injection in urethra region were excluded since neurogenic bladder was not the main cause of external urethral sphincter dyssynergia. Voiding cystourethrography (VCUG) was performed to depict the spastic neurologic bladder before injection. In cases with a positive history of vesicoureteral reflux, improvement in grading was confirmed by VCUG before further surveys.

All patients underwent recurrent clean catheterization and urodynamic evaluation as a defined standard course before BT injection. Bladder compliance during the urodynamic evaluation was measured based on earlier standardized methods [11, 12]. Demographic data, history of anticholinergic consumption, concurrent side effects or intolerance, the dosage of the injected BT were all recorded.

BT injection was performed under general anesthesia using rigid cystoscope and endoscopic needle based on previous successful studies [12]. The procedure was performed by the same trained surgeon to reduce the following performance biases in interpreting the findings. In order to inject BT into the anterior wall with a rigid instrument, a 30-degrees lens was used. After reaching out to the dome of the bladder, the lens was turned 180 degrees and the anterior wall injection was carried out. BT (trade name Dysport, Clostridium botulinum type A, Ipsen Ltd., Berkshire, SL 1 3XE, UK), was diluted with normal saline to the standard maximal dosage of 2 mg/kg per day. To specify injection sites, methylene blue was added. Maximum of 40 square-shaped areas that were 1 cm on each side and were away from the trigone of the bladder were highlighted as injection sites [13]. Approximately 10 U were injected to the posterior and anterior wall without any injection to the trigone area.

The urodynamic variables in our study included: flow rate in second two, flow time of diuresis, time of peak flow, average flow, discharged volume, maximum detrusor muscle filling pressure (cmH2O), maximum flow, acceleration, post-void residual volume, compliance, and cystometric bladder capacity.

1.2. Ethics, consent, and permissions

The trial was enrolled in Iranian Registry of Clinical Trials (IRCT) and encoded IRCT20181124041743N1. The ethical aspects were considered and approved by the related ethical committee. SBUM allocated financial supports for urodynamic evaluation before and after BT injection along with the medication and injection costs. A written consent including the aim of the study, the benefits of the procedures and the possible side effects were assigned to all parents or legal guardians.

Table 1
Descriptive results of urodynamic findings; comparing the results before and after the treatment.

	Before treatment	3 months after treatment	p Value
Flow rate in second two (ml/s)	6.6 ± 5.29	7.09 ± 5.50	0.60
Flow time of diuresis (s)	59.77 ± 86.93	48.61 ± 63.30	0.03
Peak flow time (s)	16.98 ± 17.40	15.49 ± 15.39	0.12
Flow average	7.71 ± 4.40	7.30 ± 3.30	0.32
Discharged volume (ml)	106.84 ± 47.17	128.90 ± 44.80	<0.005
Maximum detrusor muscle filling pressure (cmH2O)	86.03 ± 28.09	72.03 ± 23.40	<0.005
Maximum flow (ml)	13.87 ± 5.35	13.57 ± 4.40	0.30
Acceleration (ml/s^2)	1.25 ± 0.76	1.28 ± 0.75	0.34
Post-void residual volume (ml)	9.02 ± 8.15	5.47 ± 4.95	0.02
Compliance (ml/cmH_2O)	7.85 ± 28.29	2.12 ± 1.17	0.002
Cystometric bladder capacity (ml)	115.41 ± 48.74	134.38 ± 44.79	0.002

1.3. Analysis

SPSS software version 22 was used to analyze the data. Percentage and mean were used to describe the nominal and scale variables. chi-Square test was implemented to compare frequencies. One-Sample Kolmogorov–Smirnov test was used to check the normality assumption of different variables. To compare the constant urodynamic results before and after injection, the Student's paired *t*-test, or the non-parametric alternative was used. The significance level was considered less than 0.05.

2. Results

Twenty patients who did not respond to anticholinergic medications or could not tolerate the side effects of the treatment were entered for the final analysis. The mean age was 7.7 ± 2.02 years (range 5–13), and 13 (65%) of them were male. Of all patients, 19 (95%) used oxybutynin, and one (5%) received tolterodine. Five patients (25%) received the medication with a maximum dose of 5 mg/day, and others received 5mg twice a day. Eight (40%) patients developed drug intolerance. Seven patients (35%) experienced anticholinergic side effects during medication therapy, including flushing as the most common one with a frequency of 85.71% (6 out of 7 cases). Recalcitrant constipation was reported in only one patient.

Past medical history was positive for myelomeningocele in 18 patients. Other two girls showed idiopathic post-neuropathic bladder following surgical intervention for vesicoureteral reflux. All patients had urinary incontinence due to uninhibited detrusor contraction, whereas its frequency decreased to 75% after 3 months of injection. There was no significant effect in comparison with the baseline characteristics on post-injection improvement in urodynamic results ($p > 0.05$). One-Sample Kolmogorov–Smirnov Test showed that all characteristics were distributed normally except for the flow time of diuresis and bladder compliance. Paired T-test and the non-parametric alternative tests were used to compare pre- and post-treatment results (Table 1). Discharge volume and maximum detrusor muscle filling pressure showed the most significant changes after injection ($p < 0.005$).

3. Discussion

We evaluated the urodynamic changes after BT injection in 20 patients with neurospastic bladder. Our findings depicted a significant increase in discharge volume, along with a significant decrease in detrusor muscle filling pressure. Furthermore, our findings were indicative of

significant reduction in post-void residual volume, flow time of diuresis, compliance, along with an increased cystometric bladder capacity. Altogether, these findings were implying the possible effective role of BT in alleviating the symptoms and signs of the neurospastic bladder. However, our study failed to depict any significant improvement in flow rate in second two, flow average and peak flow time.

In a study in 2016, 22 patients with resistant neuropathic bladder who received BT regardless of the underlying reason were retrospectively evaluated if any urodynamic improvements were achieved [12]. Similar to our study, the most consumed anticholinergic drug was oxybutynin, while myelomeningocele was the most underlying disease. No surgical complication or systemic side effects were reported within 3 to 36 months of injection. Also, there was no increase in UTI occurrence. Following the non-significant response to maximum anticholinergic medications and intermittent catheterization, BT injection was administered. This study reported significant improvement following BT injection in cystometric capacity, maximum detrusor pressure, compliance, maximum detrusor muscle filling pressure, and post-void residual volume that were convergent with our study. Significant changes in discharged volume, and the flow time of diuresis, however, were not similar to our findings. All these changes can encourage advanced surveys for defining standard indexes in urodynamic investigations and result in better understanding of major criteria correlated with clinical improvement. To provide aligned data for future meta-analyses and to facilitate clinical assessment and comparison, our treatment approaches, eligibility criteria, and techniques were parallel to this standard study.

In 2014, 17 children with spastic bladder were evaluated after BT injection. Similar to our study, myelomeningocele was the most common underlying disease 11 cases among them. All patients experienced intermittent clean catheterization before BT injection, and 15 substitute with patients of them received anticholinergic treatment. The treatment was discontinued in case of the desired improvement in bladder control after BT injection, while in case of the symptoms reappearance medication began. In the mentioned study, initial achievements were assessed based on International Children Continence Society (ICCS) [14]. Further cystometric evaluation after 3 to 42 months (with a mean of 15 months) of BT injection revealed a significant decrease in maximum detrusor pressure as it was seen in our study. Besides, the mentioned study did not report any improvement in patients with poor bladder compliance; our study revealed a clinically and statistically significant decrease in compliance after injection.

On the other hand, some urodynamic indexes like flow rate in the second two or acceleration are usually assessed although they might not be directly correlated with clinical progress. In our study, similarly, these two variables did not show significant changes in the urodynamic evaluation, whereas variables such as compliance and detrusor spasticity were not only significantly altered, but also were associated with better clinical outcomes. Furthermore, maximum detrusor filling pressure and discharge volume were both significantly improved during our survey. This finding motivates additional suggestions regarding selecting better indexes for the definition of clinical improvement or comparing specific urodynamic results. Moreover, establishing definite indexes that are better-correlated with clinical improvement, seems more cost- and time-effective than measuring each parameter for its change, per se, which may not be consistent with clinical improvement.

Though BT is considered a non-invasive method, it needs recurrent injections, and long-term follow up, since it may not provide a permanent effect. Further injections might be replaced by surgical approaches like augmentation in case of achievements following the first BT injection. Surgical surveys after the first successful BT injection can be appraised in future studies to provide a decisive guide to permanent certain treatment approaches. Nonetheless, side effects, the severity of the disease, age of the patients, long-term social and economic burden of the disease and all clinical characteristics should be assessed by future meta-analyses and cohort studies to introduce the most appropriate approach for each patient [13].

4. Conclusion

Our findings depicted a significant increase in discharge volume along with a significant decrease in detrusor muscle filling pressure, after BT injection in patients with neurospastic bladder who were resistant to previous treatments. Furthermore, our findings were indicative of a significant reduction in post-void residual volume, flow time of diuresis, compliance, along with an increased cystometric bladder capacity. Altogether, these findings were implying the possible effective role of BT in alleviating the symptoms and signs of the neurospastic bladder. However, our study failed to depict any significant improvement in flow rate in the second two, flow average and peak flow time. These findings motivate additional studies towards selecting better indexes for the definition of clinical improvement and its relation with specific urodynamic results.

Ethics approval and consent to participate

The trial was registered in Iranian Registry of Clinical Trials (IRCT), encoded IRCT20181124041743N1. The ethical aspects were considered and approved by the related ethical committee of SBUM. A written consent including the aim of the study, the benefits of the procedures and the possible side effects were assigned to all parents or legal guardians.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

None of the authors have any competing interests.

Funding

SBUM allocated financial supports for urodynamic evaluation before and after BT injection along with the medication and injection costs.

Authors' contributions

Study was designed by SL and KA. The main surgeon and supervisor were LM, while AKT was the consultant professor, who revised the manuscript. SL and KA were responsible for data collection, while AV analyzed and interpreted the data. All authors read and approved the final manuscript.

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