

Success Rate and Patients' Satisfaction Following Intradetrusor Dysport Injection in Patients with Detrusor Overactivity: A Comparative Study of Idiopathic and Neurogenic Types of Detrusor Overactivity

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Purpose: To evaluate the efficacy of intradetrusor Dysport (a type of botulinum toxin type A) injection in patients with idiopathic or neurogenic detrusor overactivity, who were refractory to antimuscarinic drugs, and to compare the efficacy of Dysport injection in both groups.

Materials and Methods: Twelve patients with neurogenic detrusor overactivity (NDO) and 18 patients with idiopathic detrusor overactivity (IDO) participated in this study. All the patients received intravesical injection of 500 units of Dysport. They were followed up for 3 months after injection with maximum cystometric capacity, maximum detrusor filling pressure, and number of catheterization or pad usage.

Results: After 3 months, the mean maximum cystometric capacity increased from 109.36 ± 24.11 mL to 266.81 ± 97.18 mL ($P = .000$) in the NDO group and from 192.24 ± 36.21 mL to 272.61 ± 63.37 mL ($P = .000$) in the IDO group. The mean maximum detrusor filling pressure decreased from 48.14 ± 26.51 cmH₂O to 28.91 ± 9.01 cmH₂O ($P = .005$) in the NDO group and from 39.22 ± 9.92 cmH₂O to 29.64 ± 10.14 cmH₂O ($P = .003$) in the IDO group.

Conclusion: Intradetrusor Dysport injection improved urodynamic parameters and quality of life (QoL) in both groups significantly. We did not find significant difference in QoL or urodynamic parameters between both groups.

Keywords: botulinum toxins, type A; administratin and dosage; urinary bladder, overactive; drug therapy; adverse effects.

INTRODUCTION

Overactive bladder (OAB) is a clinical syndrome characterized by urgency with or without urge incontinence, frequency, and nocturia⁽¹⁾ with a prevalence of 11.8% worldwide.⁽²⁾ OAB has a significant effect on the quality of life in men and women suffering from this syndrome.⁽³⁻⁵⁾ Detrusor overactivity (DO) is one of the main causes of OAB and is classified into idiopathic DO (IDO) and neurogenic DO (NDO) according to the International Continence Society classification.⁽⁶⁾ Oral antimuscarinic agents are the first line treatment modality for patients with DO; however, its usage has been limited due to the adverse effects such as dry mouth or headache and their decreased efficacy in long term period as the result of up-regulation phenomenon.⁽⁷⁾ More invasive procedures such as bladder augmentation and urinary diversion pose a significant risk of morbidity and complications to the patient.⁽⁸⁾ Botulinum toxin type A (BTX-A) which is produced by clostridium botulinum, a gram positive bacteria, inhibits the release of acetylcholine at the neuromuscular junction and subsequently paralyses the muscle. The effects of BTX-A on parasympathetic nervous system was first investigated in the 1920s by Dickson and colleagues.⁽⁹⁾ Although several studies also revealed the efficacy of intradetrusor injection of BTX-A in the treatment of both types of DO which were intractable to antimuscarinic therapy,^(10,11) the data comparing the efficacy of intradetrusor injection of BTX-A in patients suffering either IDO or NDO are lacking.^(12,13) In this study, we evaluated the efficacy of intradetrusor injection of Dysport ((Reloxin/BoNT-A, Ipsen Biopharm Ltd., Wrexham, UK) in patients with IDO and NDO, and the resulting improvement in the quality of life (QoL) in both groups.

MATERIALS AND METHODS

Study Design

Our prospective cohort study was conducted from September 2010 to December 2011. Patients with symptoms of OAB and urodynamically proven IDO or NDO who were refractory to oral antimuscarinic medication for at least 3 months or those who had discontinued medical therapy due to drug side effects participated in this experimental study. Being refractory to antimuscarinic treatment was defined as no effect of antimuscarinic drugs available in Iran, i.e. oxybutynin

hydrochloride (Iran Darou Co., Tehran-Iran), and Detrusitol (Pharmacia & Upjohn SpA, Milan, Italy) during a trial for at least 3 months. Patients with history of previous bladder surgery or Botox injection, an active urinary tract infection, any anatomical anomaly of the urinary system, urinary stone or urinary tract tumors and any medical disorder such as diabetes mellitus or multiple sclerosis were excluded from the study. Besides, all female patients were examined by a gynecologist to rule out genital infection or pelvic organ prolapse or relaxation which may induce voiding dysfunction.

Pretreatment Evaluations

All the patients gave their written informed consent and were divided into IDO and NDO groups. The patients were asked to chart a 3 days voiding diary mentioning the number of voids and episodes of urge incontinence per day. In patients with spinal cord injury and associated NDO, the numbers of urethral catheterization, and pad count per day were measured. Urodynamic study was performed in both groups according to International Continence Society's recommendations,⁽¹⁴⁾ measuring parameters such as Maximum Cystometric Capacity (MCC), Maximum Detrusor Pressure on filling cystometry (MDP), and Post Void Residual (PVR) urine volume in the IDO group during urodynamic study or by bladder ultrasonography. QoL was assessed by the Incontinence Impact Questionnaire Short Form 7 (IIQ-7). Oral ciprofloxacin 500 mg (Razak Laboratories, Tehran, Iran) was administered twice daily one day before operation prophylactically in adult patients and cefexime (Zakaria Pharm. Co., Tabriz- Iran) 8 mg/kg/day in children. Patients on antiplatelet drugs were asked to stop their medication 7 days before the operation.

Injection Technique

The procedure was performed in an outpatient manner under general anesthesia in dorsal lithotomy position with some modifications in those patients with chronic spinal cord injury and limitation of hip joint motion. After cleaning and draping, 20 mL lidocaine gel 2% (Sina Darou, Tehran-Iran) was applied intraurethrally. Dysport was administered with an 11.5 French (F) Wolf rigid pediatric nephroscope (Richard Wolf GmbH, Germany). For each adult patient, 1 vial of Dysport (500 units) was administered, and the dosage for children was 20 units/kg. Each vial was diluted with 20 mL of sterile normal saline solution before injection. The mini-

Table 1. Comparison of clinical and urodynamic parameters before and after treatment in IDO patients.

Variables	Before injection	After injection	P
Mean MCC, mL	(n = 18)	(n = 18)	< .001
Mean Maximum Detrusor Pressure, cmH ₂ O	192.24 ± 36.21	272.61 ± 63.37	.003
Mean Frequency	39.22 ± 9.92	29.64 ± 10.14	< .001
Mean FDV	18.13 ± 3.45	13.3 ± 3.74	< .001
Mean IIQ7	60.87 ± 16.71	101.33 ± 45.15	< .001

Key: IDO, idiopathic detrusor overactivity; MCC, Maximum Cystometric Capacity; FDV, Mean First Desire to Void; IIQ7, Incontinence Impact Questionnaire Short Form 7.

mally invasive technique involved 20 injections at 25 units/mL per injection site into the lateral and posterior walls of the bladder while sparing the trigonal area. Then, the bladder was drained from irrigation solution and checked for any bleeding site. All patients had an indwelling urethral catheter which was removed 24 hour after the operation. The patients were observed for 2 hours after recovery from general anesthesia and then discharged with a 5 day prescription of ciprofloxacin 500 mg twice daily.

Followup

The patients were followed up 1 week after the injection to evaluate early post-operative complications or complaints. In the 12th week after operation, urodynamic study was performed to measure MCC and MDP. PVR urine volume was measured during urodynamic study or by bladder ultrasonography in IDO group. The participants of both groups were also asked to chart the 3 days voiding diary and QoL was reassessed by the IIQ-7.

Statistical Analysis

Descriptive data were evaluated by epidemiological parameters such as prevalence, mean, and standard deviation. Normality of quantitative variables (IIQ-7, clinical and urodynamic parameters) was assessed using Kolmogorov-Smirnov test. To compare normal variables between (within) IDO and NDO groups paired *t* test and for non-normal Mann-Whitney *U* (Wilcoxon test) were used. To compare categorical variables (sex, effect of drugs and adverse reactions) between groups Chi-Square test was used. *P* < .05 values was considered as statistically significant.

RESULTS

Demographic Data

Of the 38 initially recruited patients, 8 were excluded from the study considering the exclusion criteria mentioned in the study design. A total of 30 patients (15 males, 15 females) remained in the study who were divided into IDO (18 patients) and NDO (12 patients) groups. The mean age of the participants in the IDO and NDO groups were 58.03 ± 17.16 years and 43.99 ± 15.21 years, respectively which were comparable. The age range of the patients was 18 to 74 years. In the IDO group, 14 patients (77.77%) were female, and 4 (22.23%) were males. In the NDO group, 1 patient (8.33%) was female, and 11 (91.67%) were males. The mean duration of antimuscarinic consumption was 18.6 ± 14.5 months (4 to 60 months). The drugs were not effective in 14 (77.77%) patients in the IDO group, and in 11 (91.66%) patients of the NDO group. Adverse reactions as the causes of medical treatment cessation were 27.77% (5 patients) and 16.66% (2 patients) in the IDO and NDO groups, respectively.

Post-Operation Complications

In the IDO group, one (5.55%) case of urinary tract infection was detected who was treated with a course of oral antimicrobial agent according to the result of urine culture. Another patient (5.55%) developed pelvic pain one week after injection which resolved spontaneously in 3 days. In the NDO group, one patient (8.33%) developed a severe febrile urinary tract infection 3 days after injection that was successfully treated with intravenous antibiotics. None of the participants experienced acute urinary retention or significant PVR urine (in the IDO group who void themselves), generalized muscle weakness, or significant gross hematuria.

Urodynamic Parameters

Table 2. Comparison of clinical and urodynamic parameters before and after treatment in NDO patients.

	Before injection	After injection	P
Mean MCC	(n = 12)	(n = 12)	< .001
Mean Maximum Detrusor pressure, cmH ₂ O	109.36 ± 24.11	266.81 ± 97.18	.005
Mean Pad usage	48.14 ± 26.51	28.91 ± 9.01	.001
Mean IIQ7	6.16 ± 0.86	4.75 ± 1.11	< .001

Key: NDO, neurogenic detrusor overactivity; MCC, Maximum Cystometric Capacity; IIQ7, Incontinence Impact Questionnaire Short Form 7.

The urodynamic parameters are shown in Tables 1 and 2. Twelve weeks after Dysport treatment, the urodynamic study revealed a significant decrease in the mean MDP and a significant increase in MCC in both groups. Although the mean MCC was significantly different between the two groups before injection ($P = .000$), the changes in post-injection mean MCC did not differ significantly between the two groups ($P = .700$) (Figure 1). Although mean MDP before and after Dysport injection decreased significantly in each group, it did not differ significantly between the IDO and NDO groups ($P = .200$ and $.800$, respectively) (Figure 2). The mean PVR was significantly increased in IDO patients after Dysport injection from 31 mL to 82.2 mL ($P = 0.021$). Mean First Desire to Void (FDV) was significantly increased in IDO patients following the treatment from 60.87 ± 16.71 mL to 101.33 ± 45.15 mL ($P = .000$).

3-Day Voiding Diary

The results were analyzed as a mean of 3 days before treatment and 12 weeks after treatment. In the IDO group before the treatment, 6 patients (33.33%) complained of frequency and 13 of them (72.22%) complained of both frequency and urgency with urge incontinence. The mean frequency rate and mean pad count decreased significantly after treatment in the IDO and NDO patients, respectively ($P < .001$ and $P = .001$, respectively) (Tables 1 and 2).

Quality of Life

Quality of life, as assessed using the IIQ-7, improved in both groups at 12 weeks when comparing the mean IIQ-7 score after the treatment (16.22 ± 1.03) with the mean IIQ-7 score before treatment (21.64 ± 0.48), ($P = .000$). According to the IIQ-7, 10 patients (33.33%) did not respond to the treatment, and 20 (66.66%) patients responded to the treatment. Of the

non-responders, 7 patients (48.88%) were in the IDO group and 3 patients (25%) were in the NDO group; however, the difference between 2 groups was not statistically significant ($P = .400$).

Satisfaction Rate

When all patients asked about their satisfaction following the treatments, 76.91% of NDO patients and 57.93% of IDO patients were satisfied with Dysport treatment. Satisfaction rate did not differ significantly between the two groups ($P = .600$).

DISCUSSION

OAB is a prevalent condition that affects millions of people in the world.⁽¹⁵⁾ OAB symptoms including frequency and urgency, with or without urge incontinence significantly worsen the patient's QoL. Most patients and practitioners are seeking a therapeutic method which offers appropriate and durable treatment responses in addition to minimal adverse side effects. BTX relaxes the detrusor muscle by inhibiting the release of acetylcholine at the neuromuscular junction. There are seven distinct serotypes of BTX (A, B, C, D, E, F, G) but only two of them, BTX-A and B, are available for clinical use. Several studies have shown the highly beneficial effect of intradetrusor injection of BTX-A in the treatment of DO.^(10,11,16,17) BTX-B has more side effects and a shorter duration of action compared with BTX-A; however, the data on BTX-B for the treatment of DO and incontinence are limited⁽¹⁸⁾ and it is too early to determine whether it will have similar results to those with BTX-A. It has been proposed that BTX-A reduces the level of the nerve growth factor in the suburothelium and urine; a factor which can be responsible for induction of inflammatory processes or bladder overactivity.⁽¹⁹⁾ Botox and Dysport are the available products of

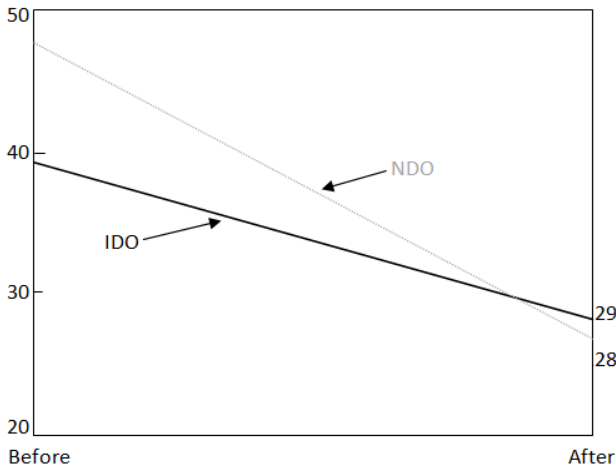


Figure 1. Comparison of mean maximum cystometric capacity before and after treatment in each group.
Key: NDO, neurogenic detrusor overactivity; IDO, idiopathic detrusor overactivity.

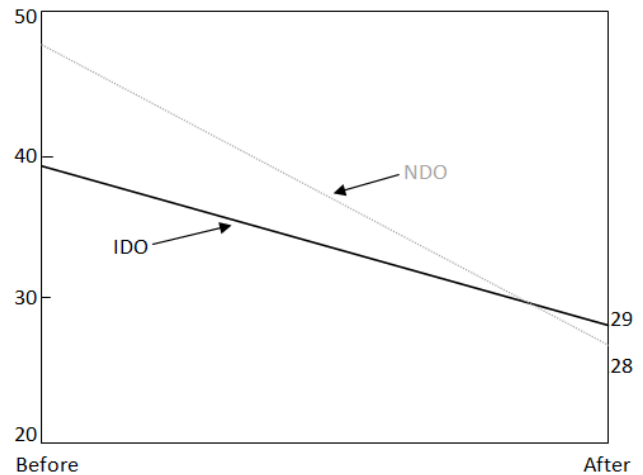


Figure 2. Comparison of mean maximum detrusor pressure before and after treatment in each group.
Key: NDO, neurogenic detrusor overactivity; IDO, idiopathic detrusor overactivity.

BTX-A which are now being used and it is suggested that each unit of Botox is equivalent to 3.5 to 5 units of Dysport.⁽²⁰⁾ To date according to published studies 100 to 400 units of Botox and 500 to 1000 units of Dysport have been used; comparison of the results of these studies shows relatively similar subjective and objective outcomes.⁽²¹⁾ In our study, intradetrusor injection of 500 units of Dysport had a significant therapeutic effect on both IDO and NDO patients who were refractory to oral antimuscarinic medications. In each group, a significant increase in MCC and a significant decrease in MDP were observed following treatment with Dysport. Comparing the urinary frequency rate before and after the treatment in IDO patients revealed a significant decrease after the treatment. The mean pad count in NDO patients who used pads within the intervals of urethral catheterizations was significantly decreased after Dysport injection. In IDO patients FDV was significantly increased following the treatment which is probably due to both increase in cystometric capacity and decrease in urgency. According to the IIQ-7, the patients' QoLs were significantly improved in both groups following the treatment and in almost all patients; changes in the urodynamic parameters were concomitant with the improvement in patients' QoLs and symptoms. Considering the mentioned results, our study confirmed the results of previous studies regarding the beneficial effects of intradetrusor injection of Dysport in patients with DO. A systematic re-

view of the role of Botox and Dysport in the management of lower urinary tract disease was conducted by Mangera and colleagues.⁽²²⁾ They found a high level of evidence for the use of Botox in children and adults with NDO or IDO, but only level 1 evidence for Dysport in adults with NDO. They also concluded that the effective dose of Botox or Dysport was different when managing IDO or NDO patients. Similar results were found in another systematic review done by Chancellor and colleagues.⁽²³⁾ However we used Dysport in both IDO and NDO adult patients with the same dosage and found significant improvements in urodynamic parameters, lower urinary tract symptoms and QoL in both groups. Our results regarding the effectiveness of Dysport in treating both NDO and IDO patients were similar to the Chancellor and colleagues review.⁽²³⁾ While most of the surveys recommend about two fold dose of Dysport to treat patients with NDO than IDO, we managed both groups with the same dose. We should keep in mind that we used 500 units of Dysport for both groups which might be more than what is necessary for treating IDO patients. Although the efficacy of BTX-A injection in the treatment of DO has been proved in different studies, the number of studies comparing the effects of BTX-A injection in the two subdivisions of DO, i.e. NDO and IDO, are lacking. Popat and colleagues followed 24 patients with NDO and 31 patients with IDO 4 weeks and 16 weeks after Botox injection and found no significant differences regarding improvement in clinical and urodynamic parameters

between the mentioned groups.⁽¹²⁾ Kalsi and colleagues compared the QoL following intradetrusor Botox injections in IDO and NDO patients and found a similar percent improvement in QoL score for both NDO and IDO groups at 4 and 16 weeks.⁽¹³⁾ Evaluating the patients' satisfaction rates following the treatment in our study revealed that the patients with NDO were more satisfied with their treatment than those with IDO (76.91% vs. 57.93%). Although this finding was not statistically significant ($P = .600$). There are several factors which could be explain the achievement of such results. First, the mean age of the patients with NDO was less than that of IDO patients (43.99 years vs. 58.03 years) which might be an explanation for a better satisfaction rate. Likewise, in a study held by Brian and colleagues evaluating the predictors of response to intradetrusor BTX-A injection in patients with IDO, it was found that younger patients with incontinence were more likely to respond.⁽²⁴⁾ The second point that should be taken into account is that the patients with NDO in our study had a higher mean MDP and a lesser mean MCC before treatment as compared to the patients with IDO (39.1 cmH₂O vs. 47.4 cmH₂O) and (101.3 mL vs. 197.4 mL). It seems that these more abnormal urodynamic parameters in NDO groups responded better to Dysport injection, causing more satisfactory results. Similarly, Sahai and colleagues in their survey found that poor responders to BTX-A injection had significantly higher MDP during DO,⁽²⁵⁾ however, a confounding factor in their study was that patients participating in that study continued antimuscarinic consumption even after BTX-A injection. With respect to the urodynamic parameters in our study, although the improvements in mean MDP and mean MCC in each group were statistically significant, comparing both groups changes did not differ significantly. Voiding dysfunction and especially urinary retention can be one of the complications after BTX-A injection which is due to the muscle paralysis caused by this substance. In a study by Stephen Jeffery and colleagues a high incidence of voiding dysfunction was reported following injection of 500 units of Dysport in IDO patients which 36% of them required catheterization in 6 weeks and 36 months after injection.⁽²⁶⁾ The incidence of retention following Dysport injection was 19% in the study held by Popat and colleagues.⁽¹²⁾ In our study, the mean PVR urine was significantly increased in IDO patients after Dysport injection from 31 mL to 82.2 mL; however,

we did not notice any episodes of urinary retention in our IDO group following the treatment and all the IDO patients voided successfully. Transient muscle weakness is another complication after Dysport injection mentioned in some studies,^(26,27,28) but this complication also was not detected in our patients. According to these results, although intradetrusor injection of Dysport was an effective treatment modality for both groups, we did not find any priority for Dysport injection between NDO and IDO patients.

Our study is not without limitations. Although neurogenic and idiopathic detrusor overactivity can cause the same clinical symptoms, their pathophysiology and severity of symptoms are different which make the comparison of both groups difficult. In our study the gender and severity of symptoms in both groups were not statistically comparable which can cause a selection bias while comparing both groups. We are also aware that some insignificant findings in our results can be due to small sample which resulted in low study power.

CONCLUSION

Considering our results and also previous studies, there is no doubt about the valuable effects of BTX-A and especially Dysport in our study in alleviating the signs and symptoms of patients suffering from DO by improving their urodynamic parameters; however, more studies are needed to compare the effects of BTX-A in NDO and IDO patients.

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CONFLICT OF INTEREST

None declared.

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