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A SINGLE CENTER, PROSPECTIVE, RANDOMIZED STUDY TO EVALUATE THE EFFECT OF REPEAT INTRADETRUSOR INJECTIONS OF BOTULINUM TOXIN-A FOR REFRACTORY IDIOPATHIC OVERACTIVE BLADDER PATIENTS: DOSE DIFFERENCE BETWEEN 100U VS 150U.

Hypothesis / aims of study
Intradetrusor injection of Botulinum toxin-A (BTX-A) is now a widely accepted second line treatment option for patients with refractory idiopathic overactive bladder (OAB) symptoms. However, the optimal dose remains to be determined. This is the first prospective, randomized trail conducted to study the efficacy of 2 dose levels of BTX-A (100U and 150U) after repeat intradetrusor injections in refractory idiopathic OAB population.

Study design, materials and methods
During a 7 year period we recruited 60 patients to take part in this institutional review board approved, investigator initiated, prospective, single center randomized trial. Patients enrolled in the study were eligible to receive 6 injections of BTX-A during the 3 year study duration, with a minimum inter-injection time period of 6 months. Each patient was randomly allocated to receive either 100U (n=30) or 150U (n=30). Subjects completed a three day voiding diary (3VD), urogenital distress inventory-6 questionnaire (UDI-6) and graded their current quality of life on a 10cm visual analogue scale (VAS) prior to study enrollment and at week 6 after every injection. The outcome analysis was based on the amount of improvement noted on the UDI-6 and VAS scores at week 6 after every injection as compared to at study enrollment. Dose difference between 100U and 150U was analyzed. The results of the injections were analyzed using T test, one-way ANOVA and Fisher's exact test.

Results
Mean age was 57 (range 23 – 83 years). There were 9 (15%) males and 51 (85%) females. The mean UDI-6 scores at study enrollment was 8.75 +/- 2.21 and 9.0 +/- 2.12 for patients randomized to receive 100U and 150U of BTX-A respectively (p-0.657). The mean UDI-6 scores at study enrollment did not differ between male and female patients (p=0.708). The mean UDI-6 and VAS scores at study enrollment and week 6 after repeat injection is illustrated in Table-1. Table-2 compares mean UDI-6 and VAS scores after repeat injections of BTX-A amongst patients randomized to 100U and 150U. The mean inter injection time interval was 6.94 months.

Table -1 Improvement in UDI-6 and VAS scores 6 weeks post BTX-A injection compared to Baseline.

Injection #	(N)	Mean Baseline UDI-6	Mean Post Injection UDI-6	Mean Baseline VAS Score	Post Injection VAS score
1	60	8.25 +/- 2.98	3.32 +/- 2.16*	9.38 +/- 1.20	3.63 +/- 2.29*
2	36	8.33 +/- 2.97	3.53 +/- 2.19*	9.25 +/- 1.38	3.75 +/- 2.50*
3	23	8.35 +/- 2.40	3.13 +/- 1.81*	9.43 +/- 1.21	3.17 +/- 2.10*
4	16	7.75 +/- 2.14	2.38 +/- 1.58*	9.63 +/- 1.02	2.56 +/- 2.06*
5	12	8.42 +/- 1.97	2.33 +/- 1.43*	9.67 +/- 1.15	1.92 +/- 1.16*
6	9	8.89 +/- 2.02	3.22 +/- 1.71*	9.56 +/- 1.33	2.67 +/- 1.22*

(*p=0.0001)

Table 2- Comparison of UDI-6 and VAS scores

Injection #	UDI-6 100 U	UDI-6 150 U	**p**	VAS- 100 U	VAS- 150 U	**p**
1	2.75 +/- 1.5	3.0 +/-0.707	**0.412**	3.75 +/- 1.893	2.20 +/- 1.789	**0.001**
2	3.75 +/- 1.708	2.40 +/- 1.517	**0.017**	4.50 +/- 1.732	2.20 +/ 1.789	**0.0003**
3	2.25 +/- 0.957	2.80 +/- 0.837	**0.156**	2.75 +/- 1.258	2.20 +/- 1.095	**0.275**
4	2.25 +/- 0.957	2.60 +/- 0.894	**0.45**	2.75 +/- 1.258	2.40 +/- 1.517	**0.624**
5	3.25 +/- 0.957	2.60 +/- 1.342	**0.377**	2.75 +/- 1.258	1.80 +/- 1.095	**0.192**
6	3.0 +/- 0.816	3.40 +/- 2.302	**0.752**	2.50 +/- 1.0	2.80 +/- 1.483	**0.740**

Interpretation of results
The mean UDI-6 and VAS scores improved significantly (p=0.0001) post injection when compared to study enrollment (Table-1). The mean UDI-6 scores after repeat injections of BTX-A did not differ significantly in patients belonging to the 100U and 150U treatment arms (Table-2). Patients randomized to receive 150U had statistically better quality of life based on the VAS scores after the 1st and 2nd injection. This effect did not last through the later injections (Table-2).

Concluding message

Repeat intradetrusor injections of BTX-A is capable of significantly improving the UDI-6 scores and improving the quality of life in patients with idiopathic OAB symptoms refractory to anti-muscarinic therapy. Long term repeat injections of both doses of BTX-A (100U & 150U) appear to be equally efficacious in improving urinary symptoms in refractory idiopathic OAB patients.

Specify source of funding or grant	**Allergan Inc, USA – Provided Botox vials and funding for the study.**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**Institutional Review Board (Human subject resource office), University of Miami. Registration # 20020122.**
Is this a Randomised Controlled Trial (RCT)?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Human subject resource office**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**