

Research Article

The Use of OnabotulinumtoxinA for Treatment of Detrusor Overactivity in Older Patients

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Abstract

Objective: To evaluate the outcomes of intra-detrusor OnabotulinumtoxinA for the treatment of Detrusor Overactivity (DO) in patients both over and under the age of 70. Our primary end points were subjective improvement, UTI and urinary retention after treatment.

Materials and Methods: A retrospective chart review of 85 male and female patients who received intra detrusor onabotulinumtoxinA for the treatment of DO was conducted. The data was analyzed by fitting generalized linear mixed models using the package 'lme4' in R. We examined the association between age over 70 years, Pelvic Organ Prolapse (POP), Neurogenic Detrusor Overactivity (NDO), catheter use, and type II diabetes (DM), with post-injection subjective improvement, Urinary Tract Infection (UTI), and retention.

Results: Subjective Improvement: Odds of reporting improvement are 83% lower in people over the age of 70 (95% CI [22%, 96%]). Odds of reporting improvement are 3.8 times higher in those with DM compared to those without DM (95% CI [0.73, 46]). Post Injection UTI: Odds of UTI are 7.6 times higher in those with NDO than in those without NGB (95% CI [1.2, 47.0]). Odds of UTI are 5.9 times greater in patient's ≥ 70 than in those under 70 years old (95% CI [0.99, 35]). Urinary retention: No significant associations were found.

Conclusion: Intra-detrusor onabotulinumtoxinA is safe and effective for patient's ≥ 70 however they are less likely to report subjective improvement of their urgency incontinence symptoms and are more likely to experience UTI after treatment than patients less than 70 years of age. These findings allow for improved counseling of older patients regarding their associated treatment risks and likelihood of symptom improvement.

Keywords: Botulinum toxin; OnabotulinumtoxinA; Urinary urge incontinence; Overactive bladder, Detrusor overactivity

Brief Summary

OnabotulinumtoxinA is effective for patient's ≥ 70 ; however they are less likely to report subjective improvement and are more likely to experience UTI.

Introduction

Overactive Bladder (OAB) syndrome includes the symptoms of urinary urgency, urgency incontinence, frequency, and nocturia [1]. The clinical symptoms of OAB correspond to unsolicited detrusor contractions on urodynamic testing, termed Detrusor Overactivity (DO). When attributed to a neurologic disorder, the condition is termed Neurogenic Detrusor Overactivity (NDO). However, in most cases no neurological explanation for patient symptoms can be found, resulting in the diagnosis of Idiopathic Detrusor Overactivity (IDO).

First line treatment for DO has traditionally consisted of conservative management with lifestyle and fluid intake modifications. Second line treatment consists primarily of anti-muscarinic medications, the use of which is limited by side effects, including dry mouth and constipation, and patient compliance [2]. Recently, intra-detrusor onabotulinumtoxinA injections have increased in popularity as a minimally invasive, highly successful

and well-tolerated therapy for all DO patients who have failed less invasive treatments [2-6].

In August of 2011, onabotulinumtoxinA was approved by the FDA for use in the treatment of DO secondary to neurogenic causes and then for idiopathic overactive bladder in 2013 [7]. This novel treatment has provided symptomatic relief for many patients with 42-87% of patients reporting complete continence after treatment, revolutionizing the treatment of DO. Despite the potential success of this therapy, possible side effects complicate its use including: prolonged urinary retention, increased post void residual, straining to void, gross hematuria, Urinary Tract Infections (UTI) and rarely, generalized weakness [8]. Risk factors for the development of possible adverse effects remain unclear, although our unit has postulated that advanced age may predict a higher incidence of associated side effects and reduced efficacy of treatment in patients undergoing intra-detrusor onabotulinumtoxinA injections. Unfortunately, most of the published studies on onabotulinumtoxinA injection into the detrusor muscle for DO enrolled limited numbers of older patients, limiting the generalizability of these studies to older patients [2,9]. As a result, the impact of age on tolerability and treatment outcomes in geriatric patients remains unknown.

The objective of our study was to evaluate the efficacy and side effects of intra-detrusor onabotulinumtoxinA injection for DO in patients aged ≥ 70 years old as compared with patients < 70 years of age.

Materials and Methods

This is a retrospective case study of all patients 18 years of age or older who received onabotulinumtoxinA intra-detrusor injections over a 5 year period between January 1, 2008 and October 31, 2013, at University Hospitals Case Medical Center in Cleveland, Ohio, for the treatment of symptoms of DO. Approval for this study was obtained from the University Hospitals Case Medical Center Institutional Review Board. Patients were identified using CPT code 53899U01 and 52000. Data was extracted from the medical charts manually and compiled into a database. Inclusion criteria included male and female patients who received intra-detrusor onabotulinumtoxinA injection for treatment of DO documented on pre-treatment urodynamics, and followed up in clinic within three months of injection. Post-treatment assessment included: post void residual measurement, and assessment of symptoms at a follow up visit.

Patients were excluded if they did not follow up within three months of injection. Those patients with indwelling catheters were not included in evaluation of post procedure urinary retention. Urinary tract infection was defined as an office urine dip or urine culture which was treated with antibiotics within 30 days of onabotulinumtoxinA injection. Urinary retention was defined as a post void residual >150 ml at the post injection visit or the need for de novo catheterization within 30 days of treatment. Data on subjective improvement was gathered from the provider's notes of the post-operative visit. During this visit, their symptoms were assessed by the provider. Patients must have reported subjective improvement and/or overall satisfaction with the treatment during their post operative visit that was then recorded in the chart to qualify as having experienced subjective improvement of their symptoms. Patients were seen and treated by four different providers in our practice. The decision for dosage of onabotulinumtoxinA was made on an individual basis by each provider regarding each patient. Each dose of onabotulinumtoxinA, ranging from 100-300 units, was reconstituted in 20 cc of sterile normal saline and was followed with a 2cc flush of sterile normal saline. All patients in clinic are routinely checked for infection by urine dip prior to treatment and prescribed 3 days of twice daily oral nitrofurantoin 100mg post intra-detrusor onabotulinumtoxinA injection or a comparable antibiotic for 3 days if allergic.

To analyze the association between age ≥ 70 years and post-injection UTI, retention and subjective improvement we fit generalized linear mixed models using the package 'lme4' in R. Mixed models were used because some patients had multiple onabotulinumtoxinA injections resulting in multiple outcome measures¹⁰. The focal predictor in our statistical models was age ≥ 70 years. In addition to age, we examined the association between Pelvic Organ Prolapse (POP), NDO, pre-injection catheter use (except when the outcome was retention), Type II diabetes (DM) and injection number, with post-injection UTI, retention and subjective improvement.

In the analysis, two statistical models were utilized. The first

Table 1: Baseline study characteristics.

	Age < 70 (n=50)	Age ≥ 70 (n=35)	P value
Gender: Male (%)	12 (14)	5 (6)	0.27
Female (%)	38 (44)	30 (41)	
NDO (%)	35 (41)	16 (19)	0.04
POP (%)	10 (14)	9 (12)	0.77
DM (%)	6 (7)	8 (9)	0.30
Catheter Use (%)	12 (14)	5 (6)	0.41
Avg BMI	30.3	32.4	0.43*
History of UTI (%)	33 (72)	23 (70)	1

All P-values are under the Chi-square test of independence (with continuity correction), except where noted.

*Mann-Whitney non-parametric

addressed age > 70 as the focal predictor and all predictor variables that could affect our outcomes including NDO, POP, pre-injection catheter use, DM and injection number. A second model was then used which removed variables that showed no association with the outcome in question. In this model we included variables from our initial model, which were statistically significant or were approaching statistical significance. Here we defined 'approaching statistical significance' to be having a p-value < 0.20 . This allowed us to control for predictor variables as well as document their association on the outcomes. Statistical significance was set to 0.05.

Results

A total of 88 charts were reviewed. One patient was excluded from the analysis due to having an outlying number of injections over the study period. Two patients were excluded for failure to follow up after treatment. Eighty-five patients were included in our analysis and could have undergone multiple injections during the study period. The majority of the injections were performed in the operating room, and those which were not performed in the operating room were performed in the office setting. When performed in the operating room, general anesthesia was used. Local anesthesia with lidocaine gel was used for office procedures. For analysis, patients were categorized into 2 groups: those ≥ 70 years old and those < 70 years old. (Table 1) shows baseline characteristics of the study population. Fifty patients were < 70 years old and 35 patients > 70 years old. Mean \pm SD age of the < 70 was 53.8 ± 11.9 years, and of the > 70 group was 76.8 ± 6.1 years. Both groups had more female than male patients; however the gender distribution across age groups was not significantly different (Table 1). Patients < 70 years old were significantly more likely to have a neurologic diagnosis.

Patients received a median of 1 (range 1-6) injections of intra-detrusor onabotulinumtoxinA, and a median of 200 (range 100-300) units of onabotulinumtoxinA toxin with each treatment for both patient age groups. The dosage was decided upon individually between each provider and their patient based on their history and symptoms. The mean number of units of onabotulinumtoxinA between age groups was not significantly different. More patients in the age under 70 groups went on to have a second treatment. The average months between injections one and two were not significantly different between age groups (Table 2).

Post-injection UTI risk

In our initial model assessing all predictor variables across all

Table 2: Results after one injection of intra-detrusor botulinum toxin.

	Age < 70 (n=50)	Age ≥ 70 (n=35)	P value
Retention (%)	9 (26)	5 (23)	1
UTI (%)	9 (19)	9 (33)	0.28
Subjective Improvement (%)	42 (84)	16 (64)	0.01 †
Reinjection (%)	28 (56)	9 (26)	0.01
Avg # of months between injections 1 and 2	12.8	10.3	0.45 *
Avg # of botox units	189	172	0.26 *

All P-values are under the Chi-square test of independence (with continuity correction), except where noted.

†Fishers exact, *Mann-Whitney non-parametric

Table 3: Odds ratio estimates for post-injection uti based on initial model.

	Estimate	Z value	Lower 95%	Upper 95%	P-value
(Intercept)	0.01	-2.04	0	0.83	0.04
Age ≥ 70	4.66	1.31	0.47	46.15	0.19
POP	2.38	0.80	0.29	19.68	0.42
DM	0.59	-0.44	0.06	6.22	0.66
Catheter use	1.40	0.26	0.11	17.48	0.79
NDO	8.72	1.94	0.98	77.22	0.05
Injection number	1.34	0.70	0.59	3.04	0.49

injections, we see that age ≥ 70 years and NDO show a tendency toward increased risk of post-injection UTI (p = 0.19 and p = 0.05, respectively), (Table 3). Other factors, including POP, DM, catheter use and injection number, show no association with post-injection UTI (0.42 < p < 0.79), (Table 2). In our final model, where variables indicating no association with post-injection UTI were removed, we see that NDO and age ≥ 70 are significantly associated with post-injection UTI risk (p = 0.03, p = 0.05), (Table 4). In this model, patients with NDO have a 7.6 times greater odds of post-injection UTI compared to those without NDO (95% CI [1.2, 47.0]). The odds of post-injection UTI are estimated to be 5.9 times higher in those 70 years of age and over compared to those younger than 70 years of age

Urinary retention

We did not find any significant associations between odds of post-injection retention and age over 70 years (p = 0.87); nor did we find significant associations between NDO, POP, DM or injection number with odds of post-injection retention (0.59 < p < 0.95), (Table 5).

Subjective improvement

We found that age ≥ 70 years shows reduced odds of post-injection subjective improvement (p = 0.08) when calculated with our initial model using predictor variables of age ≥ 70 years, NDO, POP, DM, catheter use and injection number. In contrast, DM shows increased odds of post-injection subjective improvement (p = 0.128, Table 6).

Table 4: Odds Ratio Estimates for Post-injection UTI Based on Final Model.

	Estimate	Z value	Lower 95%	Upper 95%	P-value
(Intercept)	0.02	-2.98	0	0.19	0.003
Age ≥ 70	5.89	1.95	0.99	35.09	0.05
NDO	7.61	2.18	1.22	47.35	0.03

Table 5: Odds ratio estimates for post-injection retention based on initial model.

	Estimate	Z value	Lower 95%	Upper 95%	P-value
(Intercept)	0.45	-0.83	0.07	2.97	0.40
Age ≥ 70	0.88	-0.17	0.20	3.80	0.87
POP	1.05	0.06	0.24	4.66	0.95
DM	0.84	-0.16	0.11	6.54	0.87
Neurogenic bladder	0.80	-0.32	0.20	3.23	0.75
Injection number	0.78	-0.54	0.32	1.92	0.59

Table 6: Odds ratio estimates for post-injection subjective improvement based on initial model.

	Estimate	Z value	Lower 95%	Upper 95%	P-value
(Intercept)	34.77	1.75	0.66	1844.47	0.08
Age ≥ 70	0.12	-1.73	0.01	1.33	0.08
POP	0.66	-0.45	0.11	4.04	0.66
DM	15.00	1.52	0.46	491.05	0.13
Catheter use	1.48	0.34	0.16	14.03	0.73
Neurogenic bladder	0.39	-0.92	0.05	2.90	0.36
Injection number	0.69	-0.75	0.27	1.81	0.45

Table 7: Odds ratio estimates for post-injection subjective improvement based on final model.

	Estimate	Z value	Lower 95%	Upper 95%	P-value
(Intercept)	7.73	3.15	2.17	27.6	0.002
Age ≥ 70	0.17	-2.28	0.04	0.78	0.02
DM	5.79	1.66	0.73	45.80	0.10

Catheter use, POP, NDO, and injection number show no association with post-injection subjective improvement (0.36 < p < 0.73, Table 6). In our final model, where variables indicating no association with post-injection subjective improvement were removed, we see that age ≥ 70 years is significantly associated with reduced odds of post-injection subjective improvement (p = 0.02) and DM approaches statistical significance (p = 0.10), (Table 7). In this model, the odds of post-injection subjective improvement are 83% lower in those ≥ 70 years of age compared to those younger than 70 years of age (95% CI [22% lower, 96% lower]). The odds of post-injection subjective improvement are estimated to be 5.8 times higher in those with DM compared to those without DM.

Discussion

Our data demonstrate that intra-detrusor onabotulinumtoxinA is an efficacious treatment for patients 70 years and older with DO demonstrated on pre-treatment urodynamic testing. Two thirds of the patients in our study > 70 years old reported subjective improvement in their DO symptoms after injection, and only one in four met of definition of post-treatment urinary retention or UTI. These finding support clinicians offering intra-detrusor onabotulinumtoxinA to their older patients with IDO and provide more generalizable rates of retention and UTI that can be used when was counseling this patient population.

Not surprisingly, patients over the age of 70 were less likely than those under 70 years old to report improvement from their

onabotulinumtoxinA injections; suggesting patient age should be considered prior to counseling patients about treatment with intradetrusor onabotulinumtoxinA. Our findings are similar to a small study of patients over the age of 75 that showed that onabotulinumtoxinA can be efficacious for the treatment of DO [11]. We also find that patients over 70 do report improvement, and 26% of older patients underwent re-injection after the first treatment. However, patients over the age of 70 are 83% less likely than those under 70 years old to report improvement from their onabotulinumtoxinA injections. One possible explanation for this could be that patients greater than 70 years old suffer from more severe DO symptoms so even moderate improvements gained with treatment still have less impact if they remain wet most of the time. In addition, given their advanced age, these patients may be a greater risk to suffer from mixed urinary incontinence. Although their DO symptoms may improve after treatment, their stress incontinence remains and patients may have trouble distinguishing between the two causes, leading to decreased satisfaction with the treatment overall.

Age over 70 years was shown to increase the risk of UTI possibly from decreased immunity with aging. We report the values within the 95% confidence interval range from 0.99, indicating a slight reduction in odds, to 35, indicating a strong increase in odds. This result is suggestive of a real effect ($p=0.05$), as essentially all values within the 95% confidence interval indicate an increased risk of post-injection UTI for those 70 years of age and older. We were also able to identify NDO as a significant risk factor for post-treatment urinary tract infection. It is known that patients with neurogenic bladder are more prone to urinary tract infections than the general population [12]. Instrumentation of the bladder may expose these already at-risk patients to infection causing organisms. Mouttalib et al., reported a 7.1% rate of UTI after treatment with intra-detrusor onabotulinumtoxinA in patients with NDO [13]. Interestingly, the younger cohort in this study had significantly more NDO than the older group. Despite this, age over 70 was significantly associated with UTI where age under 70 was not, indicating that age may have a strong influence on risk of UTI after treatment with onabotulinumtoxinA. This is an important finding to consider when counseling patients on treatment options, outcomes and expectations. Given the significant increased risk of infection when treating NDO patients with onabotulinumtoxinA, providers should consider the FDA guidelines for intra-detrusor botulinum toxin use recommending prophylactic antibiotics for 3 days before and after the injections. In this time of antibiotic stewardship, our group has elected to continue giving nitrofurantoin 100 mg po twice daily for three days post-treatment and reserve stronger antibiotics for when indicated with a documented UTI.

Despite urinary retention being a well known side effect of intra-detrusor onabotulinumtoxinA injection, no factors examined influenced rates of retention in this study. Overall rates of retention after injection were relatively low, however, leaving the possibility for a Type 2 error due to low incidence (Table 2). Further studies with larger numbers are indicated to investigate this outcome.

Diabetes mellitus appears to be associated with increased subjective improvement after treatment. Wang et al. showed in a

small case control study that onabotulinumtoxinA was safe and efficacious for treatment of OAB in patients who had pre-existing DM, and did not report differing rates of success between patients with DM and those without [14]. The values we report within the 95% confidence interval for the effect of DM range from 0.73, indicating a reduction in odds, to 46, indicating a strong increase in odds. This result is suggestive of a real effect, as the majority of values within the 95% confidence interval indicate increased odds of post-injection subjective improvement for those with DM. One potential explanation for this is that DM could cause neurological changes or DO to occur at an earlier age, and in this study, we find younger patients to be more likely to report improvement in their symptoms. Another theory is that DM associated DO may be more responsive to treatment with intra-detrusor onabotulinumtoxinA than age related changes associated with IDO. Despite not reaching statistical significance, these findings may be clinically meaningful, and further research with larger numbers is merited in this area.

The use of intra-detrusor onabotulinumtoxinA for treatment of DO is beneficial for many patients; however, given the serious potential complications of the treatment, it is important to select patients appropriately [2]. In looking at predictors of success or poor response, Cooperate et al., looked at the bladder histology of patients with NDO who had received intra-detrusor onabotulinumtoxinA injections [15]. Poor responders were found to have more bladder fibrosis and edema than did those who reported a good response from treatment. Histology, however, may be an impractical way to measure potential for successful treatment, as it requires a biopsy. In patients with IDO, bladder fibrosis, elevated baseline detrusor pressure, and low detrusor compliance and capacity have all been identified as risk factors for poor response to treatment [16,17]. Understanding risk factors for complications and predictors of success is important in choosing the correct treatment for a given patient.

Strengths of this study include that treatments were provided by multiple providers thereby making the findings more generalizable, although this fact may also be interpreted as a weakness of the study. Providers in this study included both female urologists and urogynecologists. We also examined multiple characteristics of the study groups were evaluated in order to identify possible interactions affecting outcomes of the study.

Limitations of the study include that our subjective improvement outcome was extracted retrospectively from patient charts; therefore we were unable to utilize a standardized validated questionnaire. The retrospective design also made it difficult to assess the degree of pelvic organ prolapse at the time of treatment. This data point was recorded as positive if the patient had a history of POP recorded in their chart. Additionally, the small size of our study group and some of the subgroups such as patients who used a catheter at baseline can make data assessment and interpretation difficult. We had significantly more patients with NDO in the age under 70 groups. Another limitation is that the dose of intra-detrusor onabotulinumtoxinA used was not standardized for all patients, potentially confounding our results. There is also potential for variation in technique between providers, as some prefer to raise a wheal in the suburothelial during injection while others inject deeper into the detrusor muscle. Depth of injection was not standardized or recorded in operative reports, making this

difficult to assess, which in turn could affect the outcomes. This study was designed as an explorative and descriptive analysis. The study population represents all of the patients in the University Hospitals System that received intra-detrusor onabotulinumtoxinA over the 5 year period for the given indications. Having differing numbers of patients in each age group could affect our power and outcomes, as evidenced by our wide confidence intervals. Given the lower number of events in our sample, particularly for UTI and retention, and thus, lower power to meet conservative significance levels, we wanted to report associations approaching statistical significance, as they can be suggestive of clinically meaningful effects. We feel that a real effect is detected in this study and that future, larger, and prospective studies will be needed to confirm our findings.

Future studies are warranted to further elucidate characteristics of patients who undergo successful botulinum toxin treatments, and to identify those who may be at higher risk for complications.

Conclusion

Intra-detrusor onabotulinumtoxinA injection is an efficacious treatment for some older patients with DO. Counseling regarding risks and expectations should be reviewed prior to treatment.

References

- Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The Standardization of Terminology of the Lower Urinary Tract Function: report from the Standardisation Subcommittee of the ICS. *Neurourol Urodyn.* 2002; 21: 167-178.
- Ginsberg D, Gousse A, Keppenne V, Sievert KD, Thompson C, Lam W, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. *J Urol.* 2012; 187: 2131-2139.
- Mahajan ST, Brubaker L. Botulinum toxin: from life-threatening disease to novel medical therapy. *Am J Obstet Gynecol.* 2007; 196: 7-15.
- Wyman JF, Burgio KL, Newman DK. Practical aspects of lifestyle modifications and behavioral intervention in the treatment of overactive bladder and urgency urinary incontinence. *Int J Clin Pract.* 2009; 63: 1177-1191.
- Yokoyama T, Chancellor M, Oguma K, Yamamoto Y, Suzuki T, Kumon H, et al. Botulinum toxin type A for the treatment of lower urinary tract disorders. *Int J Urol.* 2012; 19: 202-215.
- Soljanik I. Efficacy and safety of botulinum toxin Intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic review. *Drugs.* 2013; 73: 1055-1066.
- OnabotulinumtoxinA and the bladder. ACOG Committee Opinion. 2014; 604.
- Kuo HC, Liao CH, Chung SD. Adverse events of intravesical botulinum toxin A injections for idiopathic detrusor overactivity: risk factors and influence on treatment outcome. *Eur Urol.* 2010; 58: 919-926.
- Visco AG, Brubaker L, Richter HE. Anticholinergic therapy vs. onabotulinumtoxinA for urgency urinary incontinence. *NEJM.* 2012; 367: 1803-1813.
- Bates D, Maechler M, Bolker B, Walker S. lme4: Linear mixed-effects models using Eigen and S4. R package version 1. 2015; 0-5.
- White WM, Pickens RB, Doggweiler R, Klein FA. Short-Term Efficacy of Botulinum Toxin A for Refractory Overactive Bladder in the Elderly Population. *J Urol.* 2008; 180: 2522-2526.
- Yildiz N, Erhan B, Gunduz B, Yilmaz B, Alaca R, Gok H, et al. Neurogenic bladder in patients with traumatic spinal cord injury: treatment and follow up. *Spinal Cord.* 2015; 52: 462-467.
- Mouttalib S, Khan S, Castel-Lacanal E, Guillotreau J, De Boissezon X, Malavaud B, et al. Risk of urinary tract infection after detrusor botulinum toxin A injections for refractory neurogenic detrusor overactivity in patients with no antibiotic treatment. *BJU Int.* 2010; 106: 1677-1680.
- Wang CC, Liao CH, Kuo HC. Diabetes mellitus does not affect the efficacy and safety of intravesical onabotulinumtoxinA injection in patients with refractory detrusor overactivity. *Neurourol Urodyn.* 2014; 33: 1235-1239.
- Comperat E, Reitz A, Delcourt A, Capron F, Denys P, Chartier-Kastler E. Histologic features in the urinary bladder wall affected from neurogenic overactivity - a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. *Eur Urol.* 2006; 50: 1058-1064.
- Sahai A, Khan MS, Le Gall N, Dasgupta P. Urodynamic assessment of poor responders after botulinum toxin-A treatment for overactive bladder. *Urology.* 2008; 71: 455-459.
- Schmid DM, Saueremann P, Wergler M, Schuessler B, Blick N, Muentener M, et al. Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergic. *J Urol.* 2006; 176: 177-185.