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Eight-Year Experience With Botulinum Toxin Type-A Injections for the Treatment of Nonneurogenic Overactive Bladder: Are Repeated Injections Worthwhile?

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Purpose: To investigate the efficacy and safety of repeated botulinum toxin type-A (BTX-A) injections for patients with drug-refractory nonneurogenic overactive bladder (NNOAB) and explore factors predictive of outcome.
Methods: Data were collected from all patients receiving repeated BTX-A injections for drug-refractory NNOAB between 2004 and 2012. Trigone-sparing injections were administered under sedation with antibiotic prophylaxis. Patient characteristics including age, sex, preoperative urodynamics, injection number, BTX-A dose, complications, and patient global impression of improvement (PGI-I) scores were collected. Correlations between patient factors and outcomes were assessed by using Pearson's chi-square tests.
Results: Fifty-two patients with a mean age of 67.4 years (range, 26–93 years) received 140 BTX-A injections in total; 33 (64%), 15 (29%), and 4 patients (7%) received 2, 3 to 4, and 5 to 8 injections, respectively. Mean follow-up time was 49 months (range, 9–101 months). Nine patients developed urinary tract infection; additionally, 3 patients experienced transient urinary retention. Median PGI-I score was 2 out of 7 (interquartile range [IQR], 2). For 46 patients, the PGI-I score remained stable with the administration of each injection. Pearson chi-square tests revealed that male patients or reduced bladder compliance was associated with a higher (worse) PGI-I score. Median PGI-I scores for men and women were 3 (IQR, 1) and 2 (IQR, 1), respectively; additionally, median PGI-I scores for those with normal bladder compliance and those with reduced bladder compliance were 2 (IQR, 2) and 4.5 (IQR, 1), respectively. Median PGI-I scores and complication rates were the same in the older patient ($\geq$70 years) and younger ($<$70 years) patient cohorts.
Conclusions: Efficacy is maintained with repeated BTX-A injections. Patients including the elderly show a good degree of tolerability with a low complication rate. Male patients or reduced bladder compliance is associated with poorer outcomes.

Keywords: Botulinum Toxins; Urinary Bladder, Overactive; Urodynamics; Treatment Outcome

- **Research Ethics:** The study was performed in accordance with the Helsinki declaration.
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Overactive bladder (OAB) is defined as the presence of urinary urgency, frequency, and nocturia; with or without urge incontinence; and in the absence of urinary tract infection (UTI) or other obvious pathology. OAB may be related to neurological disorders, or it may be idiopathic [1].

While some patients respond to conservative therapies such as bladder retraining and pelvic floor exercises, a significant number of patients proceed to pharmacologic treatment, which

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typically involves the use of antimuscarinic agents. Many patients discontinue the use of the antimuscarinic agents because of inadequate efficacy and/or intolerable side effects [2,3]. Second-line treatment options for patients with OAB that do not benefit from oral drug therapy include intradetrusor injections of botulinum toxin type-A (BTX-A), sacral neuromodulation, percutaneous tibial nerve stimulation, long-term catheterization, and the more invasive third-line surgical treatments of bladder augmentation or urinary diversion [4,5]. With the various modalities available for treatment of drug-refractory OAB, an open discussion with the patient about the risks and benefits of each option is important. BTX-A is emerging as the preferred second-line option [6].

The short-term efficacy of a single injection of BTX-A in nonneurogenic overactive bladder (NNOAB) has been well established; however, there are limited data on longer-term follow-up and effectiveness of repeated injections [7-11]. Studies examining repeated BTX-A injections have shown that BTX-A remains efficacious with good tolerability and in most patients, interinjection intervals are of 9–19 months [12-16]. The schedule of the repeated injection administration is patient-driven (though not before 3 months); the patients are presented again when the last injection's effect is wearing off [17,18]. The reasons for a longer interinjection interval than the expected one and the reasons for discontinuation of repeated injections are less well elucidated and are more likely to be multifactorial in nature. The studies exploring these aspects have shown that lack of efficacy, dislike for clean intermittent self-catheterization, and loss to follow-up are the three main reasons for discontinuation of administration of further injections in patients [15,16]. Questions that remain unanswered include the influence of age, sex, and preoperative urodynamics (apart from detrusor overactivity [DO]) on the efficacy and safety of repeated BTX-A injections. The majority of efficacy studies include a study population that mostly or wholly comprises of women with no information about the possible differences between male and female patients.

In this study, we report the safety and efficacy of the first Australian series of patients receiving up to eight repeated BTX-A injections for NNOAB with an average follow-up period of greater than 4 years. Additionally, we report the influence of age, sex, and preoperative urodynamic factors on the efficacy of BTX-A.

MATERIALS AND METHODS

Data were collected from all the patients who received two or more injections of BTX-A for NNOAB at Concord Hospital from 2004 to 2012. All the patients had failed a trial of at least two oral anticholinergic medications. Preoperatively, all the patients underwent urodynamic assessment according to the International Continence Society standards [1]. Prior hospital drug committee approval was obtained for the use of BTX-A for patients with NNOAB. Additionally, informed consents of the patients were obtained by the treating urologist prior to each injection's administration. Further, all the patients received a prophylactic dose of intravenous antibiotic during the procedure (gentamicin was not used because of its inhibitory synergistic effects with BTX-A). Three consultant urologists and fellows (under the direct supervision of a urologist) administered the injections. Injections were administered cystoscopically (at a concentration of 10 U/mL) to the base of the bladder using a template technique sparing the trigone [17,18]. This was done under sedation/light general anesthesia. Efficacy was measured using the patient global impression of improvement (PGI-I) scoring system. PGI-I scores were obtained at follow-ups of 6–8 weeks post injections. When patients felt that the effect of their BTX-A injection was wearing off, they were presented again and the next injection was scheduled. Urodynamic tests were not routinely performed between each injection's administrations. Information regarding patient's sex, age, preoperative urodynamics, injection number, BTX-A injection dose, PGI-I scores post injection, and complications were collected. Statistical analysis was performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA), and categorical variables were compared using Pearson chi-square test. Median PGI-I scores for subgroup analyses were compared using a nonparametric Pearson chi-square test. This study was performed in accordance with the Helsinki declaration.

RESULTS

Fifty-two patients (37 women and 15 men) with a mean age of 67.4 years (range, 26–93 years) received two or more injections. This accounted for a total of 140 BTX-A injections. Of the 52 patients, 33 (64%) received 2 injections, 15 (29%) received 3 to 4 injections, and 4 (7%) received 5 to 8 injections.

On performing urodynamics, 45 patients (87%) had DO, 4 patients (8%) had reduced bladder compliance, and 3 patients

Table 1. Comparison of patients who received 2 injections with those who received three or more injections (n = 52)

Variable	2 Injections	≥ 3 Injections
No. of patients	33	19
No. of injections	66	74
Dose of BTX-A (unit), mean ± SD	174 ± 43	196 ± 52.8
Sex Men:women (ratio)	10:23 (0.43)	5:14 (0.36)
Age (yr), mean (range)	64 (26–85)	73 (47–96)
Reduced bladder compliance	4	0
Absent DO	4	0
PGI-I score, median (IQR)	2 (2)	1 (1)

BTX-A, botulinum toxin type-A; SD, standard deviation; DO, detrusor overactivity; PGI-I, patient global impression of improvement; IQR, interquartile range.

Table 2. Number and dose of BTX-A injections by year

Year	No. of BTX-A injections			Average dose (unit)
	100 Units	150–200 Units	> 200 Units	
2004	0	3	0	200
2005	1	2	1	200
2006	0	9	0	194
2007	0	6	1	214
2008	0	15	1	200
2009	2	17	2	188
2010	6	25	1	173
2011	1	18	2	192
2012	8	14	4	169

BTX-A, botulinum toxin type-A.

(6%) had increased bladder sensation during the filling phase. The average maximum fill volume was 317 mL (range, 84–500 mL). Twenty-one patients (40%) were incontinent at the time of urodynamics. Table 1 shows a comparison of patients who received only 2 injections and those who received 3 or more injections.

Average time between injections was 14.9 months. Mean follow-up time was 49 months (range, 9–101 months). The doses administered by 19 (14%), 26 (18%), 84 (60%), 2 (1%), 8 (6%), and 1 BTX-A injection (1%) were of 100, 150, 200, 250, 300, and 400 units, respectively. During the study, the number of patients receiving repeated injections increased, and the average dose of BTX-A administered gradually decreased (Table 2).

During the follow-ups, 3 patients died because of unrelated causes and 5 patients developed neurological conditions (2 cerebrovascular accidents, 2 Parkinson disease, and 1 multiple sclerosis). Of the 52 patients, 8 (15%) were recommenced oral anticholinergic medications with BTX-A injection administration. Nine patients (7% of all injections – I mean 7 of the 140 injections included in this study) developed UTI (Clavien-Dindo classification II); additionally, 3 of them experienced transient urinary retention (1% of all injections) requiring catheterization of less than 2 weeks (Clavien-Dindo classification III). Of these 9 complications, 6 occurred in the patients who received 200 units of BTX-A; the remaining three events occurred in patients receiving either 150 or 200 units of BTX-A. There were no episodes of urosepsis.

Table 3. Comparison of male and female subgroups (n = 52)

Variable	Women (n = 37)	Men (n = 15)
No. of injections	100	40
Mean dose of BTX-A (unit)	174 ± 45	212 ± 50
Mean age (yr)	67.6 ± 14.6	67.3 ± 17.0
Detrusor overactivity	35 (95)	12 (80)
Reduced compliance	2 (5)	2 (13)
Mean max fill volume (mL)	304 ± 125	372 ± 173
Incontinence at urodynamics	9 (24)	2 (13)
PGI-I score, median (IQR)	2 (1)	3 (1)
Complications, No. of injections (%)		
UTI	5/100 (5)	1/40 (3)
UTI + retention	1/100 (1)	2/40 (5)

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
BTX-A, botulinum toxin type-A; PGI-I, patient global impression of improvement; IQR, interquartile range; UTI, urinary tract infection.

Median PGI-I score was 2.0 out of 7.0 (interquartile range [IQR], 2). For 46 of the 52 patients, the PGI-I scores remained stable with the administration of each injection. PGI-I scores improved and worsened by one point in two and four patients, respectively.

Pearson chi-square tests were performed to assess the correlation between PGI-I scores and several variables including patient age, sex, presence of reduced bladder compliance, presence of incontinence at the time of performing urodynamics, and absence of DO. A significant relationship was found between PGI-I scores and patient's sex and presence of reduced bladder compliance. Male patients or reduced bladder compliance was associated with a higher (worse) PGI-I score.

When the results are analyzed by sex, the median PGI-I

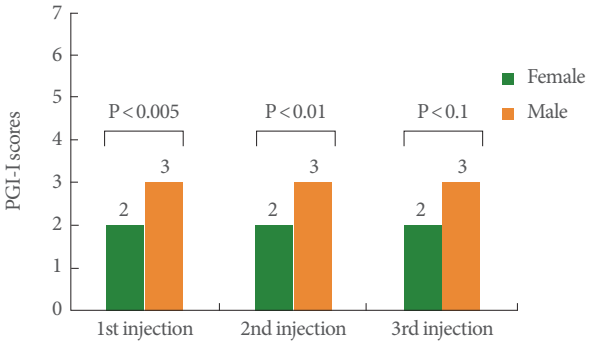

Fig. 1. Median patient global impression of improvement (PGI-I) scores by sex and injection number.

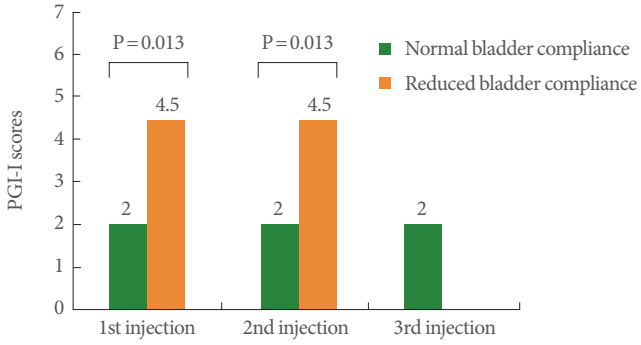

Fig. 2. Median patient global impression of improvement (PGI-I) scores by bladder compliance and injection number.

scores for women and men were 2 (IQR, 1) and 3 (IQR, 1), respectively. Baseline characteristics between both the groups are similar (Table 3). A statistically significant difference in PGI-I scores between male and female patients is present at the first and second injection administration; however, no difference is seen at the third injection administration; P=0.005 for the first injection, P=0.01 for the second injection, and P=0.1 for the third injection (Fig. 1).

There were 4 patients, that is, 2 men and 2 women, with reduced bladder compliance. The median PGI-I score for patients with reduced bladder compliance was 4.5 (IQR, 1) and for those with normal bladder compliance was 2 (IQR, 2). A statistically significant difference in PGI-I scores between those with reduced bladder compliance and those with normal bladder compliance is present at the first and second injection administration; P=0.013 for the first injection, and P=0.013 for the second injection (Fig. 2). No patients with reduced bladder compliance received a third injection.

Of the 52 patients, 28 (54%) were 70 years or older in age,

Table 4. Comparison of younger (<70 years) and older patients (≥70 years) (n=52)

Variable	<70 yr (n=24)	≥70 yr (n=28)
Sex		
Men:women	9:15 (0.6)	7:21 (0.3)
No. of injections	60	80
Mean dose of BTX-A (unit)	184	182
Mean time between injections (mo)	14.8	15.8
Detrusor overactivity, n (%)	19 (79)	27 (96)
Reduced compliance, n (%)	2 (8)	2 (7)
Mean maximum fill volume (mL)	380	277
Incontinence at urodynamics, n (%)	1 (4)	10 (36)
PGI-I score, median (IQR)	2 (1)	2 (3)
Complications, No. of injections (%)		
UTI	2/60 (3)	4/80 (5)
UTI+retention	1/60 (2)	2/80 (3)

BTX-A, botulinum toxin type-A; PGI-I, patient global impression of improvement; IQR, interquartile range; UTI, urinary tract infection.

and 80 of the 140 injections (57%) were administered to patients that were 70 years or older in age. Median PGI-I scores in the younger and the older groups were 2 (IQR, 1) and 2 (IQR, 3), respectively. There was no statistically significant difference at any time point between the 2 groups; P=0.3 for the first injection, P=0.4 for the second injection, and P=0.8 for the third injection. Complication rates were also similar. Table 4 shows a comparison of baseline characteristics, outcomes, and complication rates of younger versus older patients.

DISCUSSION

Drug-refractory NNOAB represents a common clinical problem, and its frequency is expected to increase in an ageing population. BTX-A is being increasingly used for this indication. Given that each BTX-A injection is expected to provide temporary relief, repeated injections are used increasingly for the management of OAB. Therefore, ensuring safety and efficacy of repeated injections is important.

With a median PGI-I score of 2.0, our study shows that in patients with drug refractory NNOAB, repeated BTX-A injections provide an effective therapeutic option. Overall, for each patient, the PGI-I score remained stable with the administration of each injection; it only worsened by one point in 4 patients and in 4 of the 140 injections administered. The PGI-I score stability with each repeated injection suggests that efficacy

is maintained, and patients' initial response to BTX-A is likely to be a good predictor of their response to future injections. These findings are consistent with that of the other published data exploring this question [12-15]. In this patient cohort, the time between injections is also comparable to that of the other published studies [15,16].

Our study showed that there was no significant relationship between patient age and efficacy based on PGI-I scores. Additionally, there was no increase in complications in the older patient cohort (≥70 years of age) compared to that in the younger patient cohort (<70 years of age). This is of particular relevance given that the older patients are more likely to have overactive bladder and are more likely to be intolerant to the side effects of oral anticholinergic medications. In our cohort, almost two-thirds of all the injections were administered to patients aged ≥70 years. This is likely to reflect our local patient demographics, given the fact that Concord Hospital was previously a repatriation hospital. Our findings support not only the efficacy but also the safety of repeated BTX-A injections in the elderly; additionally, advanced age should not necessarily be a factor for exclusion from repeated BTX-A injection administration. Only one other study, to our knowledge, focuses on this patient population. The study included 21 elderly patients aged 75–92 years and showed good short-term efficacy and tolerability after a single injection of BTX-A was administered [19].

Male patients or reduced bladder compliance was associated with a higher (worse) PGI-I score. While this study does not give an explanation as to why this may be the case, it is the first to make this observation.

One of the limitations of this study stems from the study population. As the aim of the study was to assess safety and efficacy of repeated injections, only those patients who had received some degree of benefit (even if small) from the first injection would have been considered for a repeated injection, that is, this cohort assesses those who were likely to be responders to BTX-A rather than the nonresponders. In spite of this selection bias, there were no patients with reduced bladder compliance that received a third injection; additionally, median PGI-I score of 4 (no difference) was observed because of the lack of efficacy and these patients did not receive further injections.

Additionally, male patients were associated with a higher PGI-I score. The authors propose that the higher PGI-I scores in the male patients as opposed to those in the female patients may be because of the added complexity of the prostate pathology. The enlarged prostate would result in bladder outlet obstruction. While preoperative urodynamics should detect bladder outlet obstruction, occult obstruction under the artificial circumstances of a urodynamic assessment may not detect the minor yet chronic degrees of obstruction.

In response to stretch induced by bladder outlet obstruction, the bladder epithelial and smooth muscle cells undergo changes in gene expression and protein synthesis. These processes lead to many ultrastructural changes [20,21]. In an informative study by Mirone et al. [21] using light and electron microscopy, the morphology of the normal bladder was compared to that of the ageing bladder and that of the obstructed bladder. In contrast to the normal bladder where the smooth muscle cells were closely packed together with very little intervening connective tissue, the obstructed bladder showed decreased nervous innervation, more widely displaced muscle cells with large increases in connective tissue mass, and contractile function loss of the myocytes. Interestingly, the ageing unobstructed bladder did not demonstrate any of these changes; it had the same appearance as that of the normal bladder [22]. In addition, several studies have also shown a direct relationship between reduced bladder compliance and increased passive urethral resistance and bladder outlet obstruction [23,24]. Given the histologic changes associated with bladder outlet obstruction, one would not expect the obstructed bladder to respond in the same way to BTX-A as the histologically normal bladder would. These findings are in accordance with our clinical observations that male patients or reduced bladder compliance results in a less favorable response to BTX-A. A recently published study assessing the efficacy of BTX-A in male patients with NNOAB also demonstrated a poor response to BTX-A in those with a history of bladder outlet obstruction requiring transurethral resection of the prostate [25].

No significant difference between the male and female patients from the third injection onwards is most likely explained by selection bias: only those patients who did benefit from the second would have gone on to have a third injection whilst those who did not benefit from the third injection would have been 'excluded' from going on to have a third injection. This is reflected in the fact that the ratio of men to women was lower in those receiving three or more injections than in those receiving 2 injections (Table 1).

Further limitations of our study include the retrospective nature of the study, relatively small patient number, and that efficacy was based on a subjective measure (PGI-I score). To our

knowledge, there are only two other published studies that have assessed repeated BTX-A injections in NNOAB with a larger patient population [16,26]; additionally, a study by Sahai et al. [13] showed improvements in the urodynamic parameters with up to three repeated injections. The remaining identified studies used a subjective measure of efficacy [13-16,26]. Given that OAB is a symptom complex rather than a urodynamic diagnosis, using improvement in symptoms (rather than a change in urodynamic parameters) as a measure of outcome is felt to be appropriate. A further limitation is that while a multivariate analysis would have been ideal, owing to the small patient numbers, only univariate analyses were performed.

This study demonstrated a low occurrence of complications, that is, a UTI rate of 6.4% and urinary retention rate of 2% with a good degree of tolerability and acceptance in the elderly.

In conclusion, while repeated intradetrusor BTX-A injections in patients with drug-refractory NNOAB were safe and effective, male patients or reduced bladder compliance might not respond as favorably. Patients including the elderly showed a good degree of tolerability, and complications including UTI and urinary retention were uncommon. Patients showed that global improvement in symptoms and efficacy was maintained with repeated BTX-A injections.

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