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The Use of Botulinum Toxin A in Idiopathic Overactive Bladder Syndrome

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Abstract Overactive bladder syndrome continues to be a significant burden for the general population. Current first-line medical therapy often includes antimuscarinic medications designed for overactive bladder. Poor efficacy and significant side effects of these antimuscarinic medications have left patients and physicians looking for alternative treatments. There is increasing evidence that intradetrusor injection of botulinum toxin A can effectively treat these patients. We present a current and extensive review of the literature covering the use of botulinum toxin A in patients with overactive bladder with or without idiopathic detrusor overactivity.

Keywords Botulinum toxin A · Botox · Dysport · Idiopathic detrusor overactivity · Idiopathic overactive bladder · Overactive bladder syndrome

Introduction

Prevalence and Economic Burden of Overactive Bladder

The International Continence Society defines overactive bladder (OAB) as "urgency, with or without urge incontinence, usually with frequency and nocturia, with no proven infection or other obvious pathology" [1]. The prevalence of OAB in the United States has been determined to be 16% (approximately 34 million) among the general population, with both men and women being equally affected. However, the severity of symptoms differed significantly based on age and gender. The prevalence of urge incontinence increased from 2% to 19% in women after the age of 44 years, and from 3% to 9% in men after the age of 64 years [2]. The annual cost incurred by a person with OAB was $1925 in 2007. This corresponds to $65.9 billion for the entire OAB population. The projected cost to manage OAB in 2015 and 2020 has been estimated to be $76.2 billion and $82.6 billion, respectively [3].

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Guidelines in the Treatment of Overactive Bladder

Based on the algorithms constructed by The International Consultation on Incontinence (ICI) and the European Association of Urology, the treatment of OAB has been divided into first-line and second-line treatment. First-line treatment includes lifestyle modification, pelvic floor exercises, and bladder retraining, along with the use of antimuscarinic medication as required. Second-line treatment involves augmentation cystoplasty, urinary diversion, and less invasive sacral neuromodulation and intradetrusor injection of Botulinum toxin-A (BTX-A [4•]. Recent meta-analysis of many randomized controlled trials proved that antimuscarinic medications are more effective than placebo in treating OAB [4•]. However, the compliance among patients to continue therapy has been severely limited due to intolerable side effects and lack of efficacy [4•, 5•]. Studies report that 42% of patients discontinue therapy after 4 months, and at 1 year this increases to 77% [4•]. Based on the ICI guidelines, patients with poor response after 3 months of therapy with an antimuscarinic agent should be escalated for second-line management. Generally, in practice, less invasive and reversible sacral neuromodulation and intradetrusor BTX-A are preferred options before considering irreversible augmentation cystoplasty and urinary diversion.

History and Mechanism of Action of Botulinum Toxin A

Over the past decade, BTX-A has gained wide diffusion in the treatment of OAB [6]. Since the first reported case of food-borne botulism in the late 18th century, the therapeutic importance of BTX-A has been evolving constantly. It was not until 1895 that *Clostridium botulinum* was discovered to be the causative organism of botulism [7]. After the isolation of the toxin in crystal form in 1946 [6], Alan B. Scott and Edward J. Schantz were the first to use BTX-A in the treatment of strabismus in the early 1970s. Since then, the toxin has been widely used to treat a variety of medical conditions: muscular hyperactivity, glandular hypersecretion, pain, and most recently, OAB [7]. BTX-A binds to the receptors on the membrane of cholinergic nerves, and is internalized into the cytoplasm of the nerve ending through endocytosis. Once internalized, the toxin cleaves the synaptosomal-associated protein (SNAP-25), which prevents the binding of acetylcholine vesicles to the presynaptic membrane; this results in temporary chemodenervation and muscle relaxation [6].

Administration of Botulinum Toxin A in Patients with Idiopathic Overactive Bladder

Intradetrusor injection of BTX-A can be administered via a rigid cystoscope [8] and a flexible cystoscope [9•, 10, 11•, 12]. Patients undergoing BTX-A injection via a rigid cystoscope require the use of general or spinal anesthesia [8] as compared to local intravesical instillation of 2% lidocaine in patients having the injection administered via a flexible cystoscope [10•]. Cohen et al. [10•] evaluated the pain scores in 27 patients undergoing sedation-free flexible cystoscopy for intradetrusor BTX-A injection. They reported that in 22 female patients, the mean pain score was 3.1 (range 1–10) during the procedure and 0.7 (range 0–7) 15 min after the procedure. Likewise, in five male patients, the mean pain scores during and 15 min after the procedure were 1.6 (range 0–3.5) and 0.0, respectively. Owing to the low cost, safety, and tolerability of the sedation-free flexible cystoscopy technique to administer BTX-A in patients with idiopathic OAB, the use of rigid cystoscope is falling out of favor.

Currently, there is no published consensus over the dose, volume, depth, number, and location of injections for intradetrusor administration of BTX-A [4•]. Similarly, the method of reconstituting BTX-A also has differed among different studies. Most studies have reported diluting 100 U of BTX-A with 10 mL of 0.9% normal saline, capable of delivering 10 U/mL of BTX-A per injection [10•, 12, 13•, 14]. However, alternative reconstitution regimens exist. Brubaker et al. [9•] and Flynn et al. [11•] reported reconstituting 100 U of BTX-A with 3 mL of 0.9% normal saline. Kuschel et al. [15] reported diluting 100 U of BTX-A with 30 mL of saline. Dilution of 100 U of BTX-A with 20 mL of saline and 5 mL of saline also are reported in literature [16]. Doses ranging from 100 to 300 U have been injected in patients with idiopathic OAB with encouraging results [10•, 13•, 17•].

Intradetrusor BTX-A injections commonly are administered to the posterior and lateral walls of the urinary bladder excluding the dome and the trigone [10•, 12, 13•]. Injecting the dome generally is avoided because the bladder wall is thin and there is an increased chance of bowel injury [18]. Injecting the trigone is avoided to reduce the risk of iatrogenic vesicoureteral reflux [14]. However, recent studies have shown no increased risk in injecting the trigone [18, 19]. The injections are delivered approximately 1 to 2 mm in depth into the detrusor muscle or suburothelium. Raising a submucosal bleb with each injection may facilitate the spread of BTX-A within the tissue [14, 16, 18, 20]. Increasing the number of sites being injected may aid in wider dispersal of the toxin within the urinary bladder, resulting in better outcomes. However, further studies are warranted to confirm the hypothesis.

Results

Outcomes from studies of patients with idiopathic OAB with or without idiopathic detrusor overactivity (DO) on urodynamics were compiled. Three randomized placebo-controlled trials (RCTs) exist for evaluation. The remaining data were reviewed from case studies or randomized dose-finding studies. Due to a lack of standardization, there were significant variations in doses, brands, injection techniques, follow-up, concurrent antimuscarinic use, and outcome measurement methodology throughout the literature search.

Urinary Frequency

On average, after a single injection of BTX-A, patients experienced a 40% decrease in number of daily voids (range 12%–60%) [11•, 12, 14, 21•, 22–24]. When compared to placebo, Flynn et al. [11•] did not find a statistically significant decrease in urinary frequency. This is in contrast to another RCT by Sahai et al. [12] that found a 48.5% decrease in daily voids. In this study, patients receiving 200 U of BTX-A decreased their number of daily voids from 15.4 to 7.93, compared to the placebo group, which only decreased their daily voids from 14.33 to 14.3 ($P<0.0001$) [12]. It is unclear why there was not a statistically significant decrease in the Flynn et al. [11•] RCT, but the authors speculate that the study was underpowered for this secondary end point. It is still

unclear if urinary frequency decreases with increasing BTX-A doses. From the study by Cohen et al. [21•] comparing 100 versus 150 U of BTX-A, there is a suggestion that the larger dose was able to decrease urinary frequency by a more substantial percentage in the OAB-dry group (31% vs 52%), but a lack of dose-finding studies have been unable to confirm this.

Urgency

Although most studies used a voiding diary to obtain results, only about half of these studies included the impact of BTX-A on urgency in their results. Those studies that reported urgency found a 70.5% (63%–78%) reduction in urgency episodes, and on average, 62% of the patients had no evidence of urgency after a single injection of BTX-A [12, 14, 22–24]. The single RCT that reported urgency found that BTX-A decreased urgency episodes from 11.69 to 2.48, compared to placebo, which only showed a decrease from 7.31 to 6.02 [12].

Urinary Incontinence

Significant improvements of patient-reported incontinence have been seen after a single injection of BTX-A. Some studies differentiate between stress and urge incontinence, but most studies only report total incontinence episodes and tried to exclude patients with significant stress incontinence from study enrollment. Investigators have found a 72% (51%–91%) reduction in the number of incontinent episodes that patients experience after injection [9•, 11•, 12, 14, 23]. Furthermore, 63% of patients report complete continence after a single injection [22–25]. More objective measurements have seen a 40% decrease in pad weight and a decrease from 5 pads/day to 1.5 pads/day after BTX-A treatment [11•, 14, 22].

Urodynamic Parameters

Initial reports on patients with spinal cord injury showed substantial changes in urodynamic parameters including improved cystometric capacity and bladder compliance (BC). Patients with idiopathic OAB also have significant changes in their urodynamic parameters after BTX-A. Most notable is an increase in maximum cystometric capacity (MCC) of 145 mL or a 47% increase. The maximum detrusor pressure ($Pdet_{max}$), defined as the maximum pressure during phasic or terminal DO, decreased from 73 cm H_2O to 33 cm H_2O. This also was accompanied by a decrease in the $Pdet_{max}$ from 63 cm H_2O to 31 cm H_2O. First desire to void occurred on average 69 mL later than before BTX-A injection [12, 14, 22–24].

Quality of Life

Measurable improvements in clinical parameters do not always translate into improved patient satisfaction. Validated questionnaires have been developed to help standardize the subjective bother of urinary symptoms and incontinence into objective data. Using a visual analogue scale to measure improvement in quality of life (QOL), patients on average reported a score of 8.9 before treatment and 4.2 after treatment, with a lower score indicating less bother from symptoms [21•, 22]. More elaborate scales specific to urinary symptoms including the Urinary Distress Inventory-6 (UDI-6), King's Health Questionnaire (KHQ), and the Incontinence Impact Questionnaire (IIQ-7) also have shown that BTX-A provides significant improvement in QOL. All three RCTs found a significant improvement of QOL for BTX-A over placebo. Sahai et al. [20] reported improvement in QOL using the KHQ, noting significant improvement in favor of BTX-A over placebo in overall score, incontinence impact, physical limitations, social limitations, emotions, and severity measures at both 4 and 12 weeks. Flynn et al. [11•] also saw a significant improvement in QOL favoring BTX-A over placebo. In their study, the BTX-A group had a score reduction of 67% and 47% for the IIQ-7 and UDI-6, respectively, compared to the placebo group, which had a 4.6% and 0% reduction in score, respectively. These findings are corroborated by additional studies, all of which show a clinically significant impact on QOL after BTX-A treatment [9•, 13, 14, 25, 26].

Repeat Injections

Decreased efficacy during repeat injections of BOTOX (Allergan, Inc., Irvine, CA) for nonurologic use previously had been seen due to suspected neutralizing antibody formation. This was seen in the old formulation, 79-11 Botox. A new formulation, BSB 2024, has been created and in use since 1997. BSB 2024 delivers a reduced protein load in hopes of minimizing antibody formation [27]. Currently, long-term follow-up on patients with idiopathic OAB receiving repeat intradetrusor injections of BTX-A is sparse. Albeit low in volume, the results of repeat injections have been encouraging. Khan et al. [13•] had 24 of their initial 81 patients receive a second injection of 200 U of BTX-A. From their results, QOL continued to be significantly improved, with no difference noted from the first injection when comparing the UDI-6 and IIQ-7 scores. Sahai et al's. [17•] data on 20 patients receiving a second injection corroborates this, showing equal improvement in UDI-6 and IIQ-7 scores when compared to the first injection. They also reported that the decrease in urinary frequency, urgency, and urge incontinence decreased to the same degree after the second injection. Furthermore,

urodynamic testing done after the second injection found an equal increase in the MCC and BC with an equal decrease in the $Pdet_{max}$ when compared to the first injection. These data also are supported by our findings when following patients up to six repeat injections. In our unpublished data, the UDI-6 and visual analogue scale scores remained the same throughout the entire study period.

Botulinum Toxin A Injection in the Absence of Detrusor Overactivity

OAB symptoms often are associated with the presence of idiopathic DO [4]. Previous studies conducted to evaluate the safety and efficacy of BTX-A injection in the refractory OAB population included only patients with DO on urodynamics [9•, 11•, 12]. However, studies indicate that most patients with symptoms of urge incontinence fail to demonstrate DO on urodynamics [28–30]. Thereby, using the presence of DO as an inclusion criterion excludes a large population of patients in need of an effective treatment. Gousse et al. [31] reported treating 32 patients with refractory idiopathic OAB in the absence of DO with BTX-A injection; results showed significant improvement in urinary frequency and urge incontinence episodes at week 12 postinjection [14, 31]. Further large-scale, double-blind, placebo-controlled studies are warranted to corroborate this finding.

Side Effects, Contraindications, and Drug Interactions

Clean Intermittent Catheterization and Urinary Tract Infection After Botulinum Toxin A

While major adverse events after intradetrusor BTX-A injection are rare, urinary tract infections (UTI) and the need to perform clean intermittent catheterization (CIC) are common enough that patients should be informed of the incidence. Reporting rates of CIC after injection is difficult because of varying BTX-A doses and inconsistent opinions on what patients necessitate catheterization. Across all doses and methods of injection, CIC was performed in 25.4% (4%–43%) of patients after a single injection [9•, 11•, 12–14, 17•, 21•, 22, 25]. Only two studies have randomized patients to different doses, either 100 versus 150 U with Cohen et al. [21•] or 200 versus 300 U from Flynn et al. [11•]. Neither of these studies found a dose-dependent relationship with the need for CIC. Studies doing repeat injections and dose titration on repeat injections have found that patients who initially required CIC after their first injection required CIC on subsequent injections. Sahai et al. [17•] tried to reduce the dose from 200 U to 150 U in four patients who required CIC after their initial injection. All four patients required CIC after their second injection with the lower dose. Three patients had a further decrease in dose to 100 U on their third injection, but two of these patients still required CIC, and the third opted to increase the dose for better efficacy. Using urodynamic calculations, Sahai et al. [32] retrospectively analyzed urodynamic variables that would predict the need for CIC. They found that the maximum urinary flow rate (Qmax), projected isovolumetric detrusor pressure (PIP1), and the bladder contractility index, were all significantly lower in the CIC group. They stated that the best predictors of CIC are PIP1 (calculated as Qmax × PdetQmax [detrusor pressure at Qmax]) for women and the bladder contractility index (calculated as 5(Qmax) × PdetQmax) for men. Using receiver operating characteristic curves to set standard values, a PIP1 of 50 had positive predictive value and negative predictive value of 42% and 94%, respectively [32].

Although a significant number of patients will experience the need for CIC after BTX-A treatment, this side effect does not appear to take away from the QOL benefit. Two studies have evaluated the QOL scores between patients requiring CIC and the rest of the study population. They found no difference in UDI-6 and IIQ-7 scores between these two groups. A likely possibility is that these questionnaires do not address CIC-related morbidity [13•, 33].

UTI was found on average in 19% (6.45%–27%) of study participants [9•, 11•, 12–14, 21•, 22, 25]. Patients performing CIC made up a significant portion of this population and likely account for the increased incidence of UTI over normal cystoscopic procedures. More serious complications after intradetrusor injections are rare. Hematuria specifically from the injection of BTX-A does not appear to be a notable risk. Generalized muscle weakness has been reported in less than 10 cases after injection of BTX-A into the detrusor or striated sphincter. All cases were transient, with effects lasting less than 2 months. This systemic side effect was usually seen with Dysport (Ipsen, Brisbane, CA) or higher doses of BOTOX [22, 34, 35].

Contraindications and Drug Interactions

Contraindications currently include prior allergic reactions, pregnancy (“category C: safety for use during pregnancy” has not been established) and breastfeeding. A relative contraindication exists for patients with neuromuscular diseases due to a possible exacerbation of generalized muscle weakness from systemic spread of the toxin. Caution should be advised when administering medications that can potentiate the neuromuscular effect of the toxin. These medications include aminoglycosides, clindamycin, magnesium salts, nondepolarizing neuromuscular blockers, quinidine, and succinylcholine. Chloroquine has the potential to have an antagonistic effect against the toxin and

interfere with the efficacy [36]. Physicians also should be aware of a current black box warning against Botox, citing its potential to spread beyond the treatment area and produce difficulty swallowing and breathing.

Conclusions

There is increasing evidence that the use of BTX-A is efficacious for patients with idiopathic OAB syndrome with or without idiopathic DO. The results of case series and two randomized placebo controlled trials have been consistent in showing that BTX-A offers significant improvement in QOL. Improvements in voiding symptoms including decreased frequency, urgency, and incontinent episodes repeatedly have been seen in these studies. Results from this review suggest that patients can expect a 40% decrease in the number of daily voids, a 70.5% decrease in occurrences of urgency, and a 72% decrease in the number of incontinent episodes. These findings are supported by the urodynamic evidence that shows improved MCC and BC while decreasing both the incidence and amplitude of DO.

Although the benefit/risk ratio appears high, almost 25% of patients across all studies had to perform CIC. Data from repeat injection and dose variation reports show that a small group of patients are hypersensitive to BTX-A and require CIC on all subsequent injections, even when the initial dose has been decreased to 100 U. Currently, dose-finding studies amongst the idiopathic DO subgroup remain sparse, and the optimal dose that provides the highest efficacy with the lowest rate of CIC is yet to be found.

An additional factor that has not been well examined is the long-term tolerability and efficacy of BTX-A injections. Well-constructed repeat-injection studies have not been published to date. For a multitude of reasons, existing reports show that 50% or less of the initial patients received repeat injections. From our own experience with repeat injections, we have seen approximately 18% of patients had complete remission of OAB symptoms after their first injection without requiring further treatment up to 3 years following treatment. About 10% drop out due to poor efficacy and 6% drop out due to need for CIC. Those patients who continue to receive repeat injections have equal efficacy when followed out to six injections.

We believe BTX-A should continue to be advocated as an effective treatment for patients with OAB syndrome. Further research should be pursued to better understand and define outcomes, appropriate doses, the patients who would benefit the most, and long-term tolerability. Once this is done, appropriate guidelines and standardization can be completed in an evidence-based method (Table 1).

Table 1 Summary of botulinum toxin A studies in patients with overactive bladder

Author	Patients, *n*	BTX-A dose	Change in frequency episodes	Change in urgency episodes	Change in incontinence episodes	Rate of CIC	Rate of UTI
Popat et al. [23]	31	BOTOX[a]: 200 U	42.6%	63%	91%	19%	6.5%
Schmid et al. [14]	100	BOTOX: 100 U	48%	No urgency in 72% at 4 weeks	No UUI in 74% at 4 weeks	4%	10%
Jeffery et al. [22]	25	Dysport[b]: 500 U	26.5%	No urgency in 33% at 1 week	No UUI in 63% at 1 week	35%	16%
Sahai et al. [12]	34	BOTOX: 200 U	48.5%	78%	60%	38%	43.7%
Mohanty et al. [24]	35	BOTOX: 200 U	60%	No urgency in 80%	No UUI in 85%	NA	NA
Brubaker et al. [9•]	43	BOTOX: 200 U	NA	NA	85.7%	27%	27%
Cohen et al. [21•]	44	BOTOX: 100 U or 150 U	43%	NA	68%	4.5%	15.9%
Khan et al. [13•]	81	BOTOX: 200 U	NA	NA	No UUI in 51%	38%	15%
Flynn et al. [11•]	22	BOTOX: 200 U or 300 U	12%[c]	NA	57%	6.7%[d]	13%

BTX-A botulinum toxin A; *CIC* clean intermittent catheterization; *NA* not available; *PVR* postvoid residual; *UTI* urinary tract infection; *UUI* urgency urinary incontinence

[a] Manufactured by Allergan, Inc., Irvine, CA

[b] Manufactured by Ipsen, Brisbane, CA

[c] Not statistically significant

[d] 27% had PVR >200 mL

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