Refractory bladder dysfunction: A multi-institutional experience with intravesical botulinum toxin-a injection in adult patients who underwent previous augmentation cystoplasty

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ABSTRACT

Objective: Augmentation cystoplasty is a treatment option for neurogenic lower urinary tract dysfunction as well as severe, refractory, complicated idiopathic overactive bladder. In some patients, symptoms may persist or recur postoperatively, and there is little guidance on management in this setting. In this study, we reviewed the use of intravesical onabotulinum toxin type A (BTX-A) in patients who had undergone augmentation cystoplasty.

Material and methods: Retrospective chart review was performed at two institutions, identifying patients who underwent augmentation cystoplasty and were subsequently treated with intravesical BTX-A. Demographics, and preoperative and postoperative findings were collected.

Results: In total, 21 (16 female, 5 male) patients (mean age: 37.2 years) with previous augmentation cystoplasty were identified. In 17 patients with urodynamic data, mean maximum cystometric capacity was 312 mL, and decreased compliance and detrusor overactivity were noted in 53% and 48% patients, respectively. Combined intradetrusor/intra-augment injections were performed in 11 patients, and the remaining 10 patients received detrusor-only injections. A total of 18 patients (86%) reported subjective improvement with no significant difference associated with site of injection (p=0.59). A total of 17 patients (77%) underwent repeat injections; on average, patients underwent 3.3 injections with interval of 8.8 months between injections.

Conclusion: BTX-A injection was shown to subjectively improve storage symptoms and continence after augmentation cystoplasty in the majority of patients. In this cohort, patients had good subjective response regardless of site of injection, and most patients benefited from repeat injections. Prospective studies are needed to better evaluate the efficacy and ideal sites of BTX-A injection in the setting of refractory voiding dysfunction following augmentation cystoplasty.

Keywords: Bladder; botulinum toxin type A; urodynamic.

Introduction

Augmentation cystoplasty is an option for management of patients with neurogenic lower urinary tract dysfunction or severe, refractory, complicated idiopathic overactive bladder (OAB). The primary goals of augmentation cystoplasty are to increase bladder capacity, maintain low detrusor storage pressures, and achieve social continence.[1] In a small subset of patients, these goals are not achieved or do not last long term following the reconstructive procedure. Unfortunately, there is little guidance on how to proceed in further management of these patients. Traditionally, if conservative measures such as anticholinergics, beta-3 agonists, and clean intermittent catheterizations fail, repeat augmentation or cystectomy with urinary diversion is performed.[1] This carries along with it the obvious risks of repeat surgery and potentially repeat failure. However, onabotulinum toxin type A (BTX-A) injection may represent a less invasive option. There is scarce data on the use of BTX-A injection in the setting of previous bladder augmentation, with one report in the literature demonstrating

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improved continence with injection into the native bladder in a patient with an augmentation cystoplasty who later required revision of his augment.[2]

In this paper, we present our experience with BTX-A injection as an adjuvant treatment in 21 adult patients from two institutions with previous augmentation cystoplasty and refractory symptoms. Our goal is to determine if there are subjective and/or urodynamic improvements with the use of BTX-A in those with refractory symptoms following augmentation cystoplasty.

Material and methods

Subjects

Institutional review board and ethics committee approvals were obtained at both institutions (protocol number PRO00012924 Houston Methodist, 12683 University of Kansas, USA). After patients' informed consent was obtained, retrospective chart review was performed at two institutions, identifying 21 adult patients with previous augmentation cystoplasty who were subsequently administered BTX-A injection. Data collected included demographic information, date of augmentation, urodynamic studies, dose, site, and timing of BTX-A injection. Subjective outcomes were also extracted from chart narratives; improvement was defined as decrease in urgency/frequency, increased catheterization volumes, and/or decreased incontinence between catheterizations.

We reviewed the available urodynamics in our patient population and identified those with detrusor overactivity as defined by the International Continence Society (ICS) as "a urodynamic observation characterized by spontaneous or provoked detrusor contractions during the filling phase which may be spontaneous or provoked"[3] and impaired compliance, defined as detrusor leak point pressure >40 cm H_2O.[4]

Statistical analysis

In those patients who were administered multiple BTX-A injections, the interval between injections was noted. Patients were given the option for repeat injection if their symptoms returned after experiencing benefit from the initial injection series. Treatment response was based on subjective symptoms at follow up (recorded in the patient's chart) or on postoperative urodynamics showing improved capacity or compliance. Characteristics of nonresponders were further analyzed, with response rate evaluated by Fisher's exact test.

Main Points:

- Injection of BTX-A into the bladder and/or bowel segment was shown to be a safe and effective treatment option in patients with refractory voiding dysfunction after augmentation cystoplasty.
- In this cohort, the majority of patients had good subjective response regardless of site of injection, and most patients benefited from repeat injections.
- Further prospective studies are needed to better evaluate the efficacy and ideal sites of BTX-A injection in this patient population.

Results

We identified 21 adult patients who underwent previous augmentation cystoplasty and received BTX-A injections following their augmentation. The majority of patients (52%) had congenital neurogenic lower urinary tract dysfunction (i.e., myelomeningocele, sacral agenesis, cloacal, or bladder exstrophy) and 28% had idiopathic OAB. The mean time to injection after augmentation was 7.8 years (0.5–26 years). Most patients (86%) presented with urgency incontinence, and 38% also complained of urgency and frequency. Table 1 outlines the baseline demographics and etiology of bladder dysfunction.

Characteristics of BTX-A Injection

BTX-A dose was determined by physician preference. A total of 13 patients (62%) received 200 units, whereas 8 patients (38%) received 300 units. In total, 10 patients received detrusor only injections, and 11 received injection both into the detrusor and intestinal augment (combined injection). A total of 17 patients (80%) received multiple BTX-A injections with an average of 3

Table 1. Patient characteristics

Patient characteristics, n=21	
	Mean (range)
Age (years)	37.2 (18–65)
Time from augmentation cystoplasty to BTX-A injection (years)	7.8 (0.5–26)
	n (%)
Gender	
Male	5 (24)
Female	16 (76)
Origin of bladder dysfunction	
Congenital	12 (57)
Spinal cord injury	3 (14)
Multiple sclerosis	1 (5)
Idiopathic	5 (24)
Presenting symptoms	
Urinary incontinence	18 (86)
Refractory storage symptoms	8 (38)

BTX-A: botulinum toxin-A

injection sessions (range 1–7). The mean time interval between injections was 10.5 months (range 2–42 months).

Urodynamic data

A total of 17 patients (81%) had urodynamic data available before their treatment with BTX-A injection. The mean cystometric capacity (MCC) was 332 mL (range 131–700 mL). Decreased capacity (<350 mL) was noted in 12 of 17 patients (70%). Impaired compliance and involuntary detrusor contractions were seen in 10 of 17 patients (59%). Of those who completed both pre and post BTX-A urodynamics (four patients), there was a minimal increase in capacity from 212 to 276 mL. Of these, three-fourths (75%) had improved compliance after BTX-A injection, with the other patient maintaining normal compliance.

Outcomes

On follow-up, 18 patients (86%) reported subjective improvement, indicated by decrease in urgency, frequency, increased catheterization volumes, and/or decreased incontinence between catheterizations. Subjective improvement was noted in 80% of those who underwent detrusor only injection and in 91% of those who underwent combined injection. Subjective improvement for those injected with 200 units compared with 300 units was 85% and 87%, respectively. There were no adverse events related to systemic absorption of BTX-A.

There were three patients who did not report subjective improvement and were classified as nonresponders. Two of these patients had myelomeningocele and one had spinal cord injury. One patient had combined injection and two had intradetrusor injection only. There was no difference in response associated with site of injection between responders and nonresponders (p=0.59). The baseline MCC of the nonresponder group was 301 mL (range 232–350 mL) versus 316 mL (range 131–700 mL) in those who responded to injections (p>0.05). One patient in this series went on to have repeat augmentation cystoplasty. Figure 1 depicts a fluoroscopic image from her videourodynamic study, showing hourglass configuration of her augmentation cystoplasty.

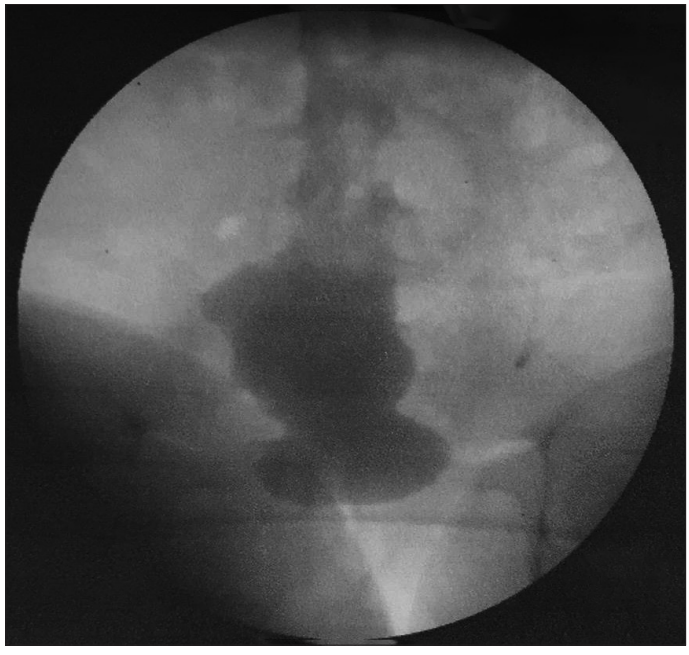

Figure 1. Fluoroscopic image from videourodynamic study of a subject showing hourglass configuration postaugmentation

Discussion

Historically, augmentation cystoplasty has been the mainstay in management of neurogenic lower urinary tract dysfunction refractory to conservative measures. Specific goals in this population include increasing bladder capacity and reducing bladder pressures to prevent upper tract deterioration as well as trying to achieve social continence.[1] In rare cases, augmentation cystoplasty or urinary diversion may be considered in severe, refractory, complicated idiopathic OAB patients per the American Urological Association (AUA) guidelines.[5]

Long-term success of augmentation cystoplasty has been well-documented in the literature, with overall continence rates ranging from 80% to 100%.[6] Additionally, augmentation cystoplasty has been shown to increase maximum cystometric capacity, reduce mean maximum detrusor pressure, and improve quality of life.[7-9] In patients with persistent or recurrent incontinence, evidence of upper tract deterioration, or recurrent infections, augment failure may be suspected and further assessment with urodynamic testing is warranted to evaluate bladder capacity and compliance.[1] In our cohort, 70% of patients had decreased capacity (<350 mL), and 59% had impaired compliance based on available urodynamic data. Potential etiologies of augment failure include inadequate size of the bowel segment, tension on the bowel mesentery, retained peristalsis of the bowel segment, and contracture of the enterovesical anastomosis, which may be seen as an hourglass configuration on fluoroscopic studies.[1] In the setting of persistently high detrusor pressures, first-line management consists of anticholinergic therapy and/or beta-3 agonist in addition to increasing frequency of catheterization.[10] Traditionally, reaugmentation would be warranted if these conservative measures fail.[11]

In the overall management of neurogenic lower urinary tract dysfunction as well as idiopathic OAB, BTX-A has emerged as an alternative treatment for patients who fail conservative medical management, before proceeding with augmentation cystoplasty. There are clear data showing significant urodynamic and subjective improvements after administration of BTX-A injections in the neurogenic population with either 200 or 300 units.[12,13] Long-term data show that the mean duration of efficacy of

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intravesical BTX-A is 6–9 months.[12] Our cohort of patients appeared to have longer efficacy with an average repeat injection time of 10.5 months (range 2–42). With the proven benefit of BTX-A injections in the native bladder, we set out to determine if there is any benefit in those who developed symptoms after their augmentation cystoplasty.

Results from our study show that BTX-A may have a similar intermediary role in management of refractory voiding dysfunction following augmentation cystoplasty. The majority of patients (86%) reported symptomatic improvement after at least one dose of BTX-A, and 81% went on to have at least one repeat injection. There was a trend toward smaller bladder capacities in the three patients who were nonresponders. There was no difference in outcomes related to dose or site of injection. The small capacity of the native bladder in some patients limits the surface area to inject. Injecting the bowel segment of an augmented bladder is thought to disrupt peristalsis in the bowel segment, leading to improved capacity and compliance.

A case reported highlighted the use of BTX-A after two previous bladder augments in the same patient.[2] This was a 49-year-old male with an ileocystoplasty conducted 14 years ago, who subsequently had a repeat augmentation cystoplasty three years later due to refractory detrusor overactivity and urgency incontinence requiring condom catheter. To avoid the risk of generalized muscle weakness from systemic absorption, the authors injected 200 units of BTX-A into the native detrusor only. The patient had an excellent outcome and became continent for the following 11 months.

In addition, there has been a case series reporting the use of BTX-A (100–200 units) in four patients with overactive orthotopic neobladder.[13] The authors utilized a minimal depth of needle penetration into the neobladder mucosa (2–3 mm) to decrease the risk of bowel injury or perforation. In this study, there were no significant adverse events with injection of BTX-A into a bowel segment. These findings are also corroborated by other studies showing safe use of BTX-A in other areas of the gastrointestinal tract, such as injection into the pyloric sphincter for the treatment of gastroparesis in Parkinson's disease [14] and injection into the anal sphincter for obstructive defecation in patients with Hirschsprung disease.[15]

We recognize there are limitations to the paper. These include bias associated with retrospective reviews and the subjective nature of our outcomes. Another limitation includes the lack of post BTX-A injection urodynamic evaluations. The main complaints of these patients are their subjective symptomatology of urinary frequency, urgency, and incontinence. We based the success of the injections on the patients' subjective improvement given the presenting symptoms included urgency, frequency, and urgency incontinence.

In summary, our data show promising results regarding the use of BTX-A as adjuvant treatment for persistent or recurrent symptoms and urodynamic abnormalities after augmentation cystoplasty. Further prospective studies may better elucidate the efficacy and ideal sites of BTX-A injection in this unique treatment setting.

In conclusion, despite invasive treatment with bladder augmentation, some patients continue to have refractory storage symptoms and/or unfavorable urodynamic parameters. Our study demonstrates safety and subjective improvement with injection of BTX-A into the native bladder and bowel segment.

Ethics Committee Approval: Ethics committee approval was received for this study from the institutional review board (IRB) at Houston Methodist Research Institute (protocol number PRO00012924) and the IRB at University of Kansas Medical Center (protocol number PRO00012683).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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