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ORIGINAL ARTICLE

What is the true catheterization rate after intravesical onabotulinumtoxinA injection?

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Abstract
Introduction and hypothesis A known side effect of intravesical onabotulinumtoxinA (Botox®) injection for overactive bladder (OAB) is urinary retention requiring clean intermittent catheterization (CIC), the fear of which deters patients from choosing this therapy. In clinical practice, patients with an elevated postvoid residual (PVR) are often managed by observation only, providing they do not have subjective complaints or contraindications. We sought to determine the true rate of urinary retention requiring CIC in clinical practice.
Methods A retrospective review was performed over a 3-year period of patients who received 100 units of intravesical onabotulinumtoxinA for the treatment of OAB. Patients were seen 2 weeks after the procedure to measure PVR. CIC was initiated in patients with a PVR ≥350 ml and in those with subjective voiding difficulty or acute retention.
Results A total of 187 injections were performed on 99 female patients. CIC was required following three injections (1.6%): for acute retention in two patients and subjective voiding difficulty in one patient with a PVR of 353 ml. Following 12 injections, the patient had a PVR of ≥350 ml, and following 29 injections, the patient had a PVR of >200 but <350 ml without symptoms. CIC was not initiated in these 41 patients. None of these patients experienced subsequent retention, and all showed resolution of their elevated PVR within 8 weeks.
Conclusions In our series of 187 intravesical injections for OAB, the rate of postprocedure urinary retention requiring catheterization was only 1.6%. This low rate can be attributed to less rigorous criteria for CIC initiation than those applied in previous studies. While important to counsel patients on the risk of retention, patients can be reassured that the actual rate of CIC is low.

Keywords Idiopathic detrusor overactivity · OnabotulinumtoxinA · Intravesical onabotulinumtoxinA injection · Urinary retention · Intermittent catheterization

Introduction

Overactive bladder (OAB) is defined by the International Continence Society as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI), in the absence of urinary tract infection (UTI) or other obvious pathology" [1]. Patients with UUI experience the urge to void immediately preceding or accompanied by involuntary leakage of urine [1, 2]. First-line and second-line treatments for OAB include behavioral modification and either anticholinergic or beta-3 agonist medication, respectively [3]. In patients with OAB who do not respond to or cannot tolerate pharmacotherapy, third-line treatments include neuromodulation or intravesical injection of onabotulinumtoxinA (Botox®; Allergan plc). In the year 2000, onabotulinumtoxinA was first shown to be effective in patients with neurogenic detrusor overactivity following spinal cord injury [4]. The vast majority of patients with UUI have detrusor overactivity without an identifiable cause. Multiple trials have similarly demonstrated efficacy of onabotulinumtoxinA for OAB [5–8].

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Randomized trials have demonstrated that intravesical onabotulinumtoxinA is as effective as oral antimuscarinic agents for lower urinary tract dysfunction, with the advantage of avoiding systemic side effects commonly associated with these medications, such as dry mouth and constipation [9]. Furthermore, over a 2-year period, intravesical onabotulinumtoxinA appears to be more cost effective than more invasive surgical options such as sacral nerve stimulation [10, 11]. In addition, recent randomized trial data suggest that intravesical onabotulinumtoxinA is associated with better daily improvement in episodes of UUI compared with sacral neuromodulation [12].

One of the most commonly reported side effects following intravesical onabotulinumtoxinA injection is incomplete bladder emptying and the need for clean intermittent catheterization (CIC). The rate of this complication has been reported to be in the range 4.5–42.8% [5, 13].The mechanism of this adverse effect is likely due to presynaptic neuromuscular blockade which induces reversible muscle weakness that may transiently impair detrusor contraction for bladder emptying [14]. However, it must be considered that although many patients retain urine, they do not necessarily need to perform self-catheterization. The clinical consequences of asymptomatic, incomplete bladder emptying after intravesical onabotulinumtoxinA treatment have not been specifically described. It also remains unclear if and/or when CIC should be initiated in these patients. Nonetheless, the relatively high reported rate of CIC following intravesical onabotulinumtoxinA injection shown in clinical trials is a common reason for patients to decline this treatment [15]. In our experience, asymptomatic patients with an elevated postvoid residual (PVR) can be safely managed by observation only, providing there are no subjective complaints or contraindications for observation. As such, we sought to determine the true clinical rate of the need for catheterization in a tertiary female pelvic medicine practice.

Materials and methods

The Cedars-Sinai Institutional Review Board approved this retrospective electronic health record review (IRB no. 00041471). Data were collected relating to a 3–year period for consecutive patients who received 100 units of onabotulinumtoxinA at a single institution in procedures performed by one of two Female Pelvic Medicine and Reconstructive Surgery (FPMRS) physicians (J.A., K.E.) for OAB. Data collected included patient demographics, body mass index (BMI), preprocedure PVR, postprocedure PVR (at 2 weeks after the procedure), postprocedure urinary retention requiring CIC, and postprocedure urine culture. Postprocedure UTI was defined as a positive urine culture with associated symptoms.

Intravesical onabotulinumtoxinA injections were performed with either a rigid 22F cystoscope or a flexible 17F cystoscope and a disposable injection needle (InjeTAK®; Laborie Inc.). Antibiotic prophylaxis was administered according to physician preference. All injections were performed in the office setting with topical anesthesia (2% viscous lidocaine). A total of 100 units of onabotulinumtoxinA diluted in 10 cm^3 of normal saline was injected into the detrusor muscle, including the trigone. The number of sites injected was at the discretion of the physician. Patients were seen 2 weeks after the procedure and the PVR was checked using a bladder ultrasound scanner and the decision to initiate CIC was made by the physician.

The primary outcomes were postprocedure urinary retention, defined as inability to void requiring catheterization, and the presence of symptomatic incomplete bladder emptying, defined as the presence of symptoms indicative of poor emptying (i.e. straining, weak stream or the sensation of incomplete emptying) with an elevated PVR of ≥350 ml. Patients with a PVR of ≥350 ml were followed every 1 to 2 weeks until PVR was <350 ml. Patient age, BMI, and preprocedure PVR were compared between those patients who required catheterization and those who did not using a paired *t*- test and the Wilcoxon rank-sum test for continuous and noncontinuous variables, respectively.

Results

During the study period, 187 onabotulinumtoxinA injections were performed in 99 female patients: 68 patients received one injection, 28 patients received two injections, and 21 patients received three injections. Mean patient age at the time of injection was 72.6 years (range 48–87 years). Mean BMI was 27.2 kg/m^2 (range 19.8–40.1 kg/m^2). Prior to injection, the median PVR was 0 ml (IQR 0–73 ml; Table 1), and following injection, the median PVR was 117 ml (IQR 58–225 ml; Fig. 1).

Following 13 of 187 injections (6.9%), the patient had a PVR of ≥350 ml. Of these 13 patients, 12 were asymptomatic and CIC was not initiated. Following 29 injections (15.5%), the patient had a PVR between 200 and 350 ml. All of these patients were asymptomatic and CIC was not initiated. Following the remaining 143 injections, the patient had a PVR was of <200 ml (Fig. 2).

In total, CIC was initiated following only three onabotulinumtoxinA injections (1.6%). One patient with a PVR of 353 ml had subjective voiding difficulty at 2 weeks. The other two patients presented with acute retention, one patient on day 1 and the other on day 2 after the procedure (Table 2).

Among the 12 patients with PVR ≥350 ml and no subjective voiding complaints of poor emptying, all were offered the option of close observation or initiation of CIC. All of these patients declined CIC and were followed every 2 weeks for assessment of PVR. None of these 12 patients had subsequent

Table 1 Baseline characteristics of study population

Variable	With retention	Without retention	*P* value
Number (%) of onabotulinumtoxinA injections	3 (1.6)	184 (98.4)	
Age at study entry (years), mean (SD)	64.7 (20.0)	72.7 (11.2)	0.223[a]
Body mass index (kg/m^2), mean (SD)	26.2 (6.5)	27.2 (6.6)	0.797[a]
Preprocedure PVR (ml), median (IQR)	0 (0–200)	0 (0–73)	0.940[b]

[a] *t* test

[b] Wilcoxon rank-sum test

acute retention. In these 12 patients, PVR decreased to <350 ml in a median of 5.8 weeks (range 4–8 weeks). None of these 12 patients required CIC for any period following injection. Among the 29 patients with PVR between 200 and 350 ml, none was offered CIC and none had subsequent acute retention. Of the three patients requiring CIC, two were able to discontinue CIC at 2 weeks after initiation, and the third was able to discontinue CIC after 1 month.

Two of the three patients (66%) requiring CIC developed an uncomplicated UTI. Of the 12 patients with a PVR >350 ml in whom CIC was not initiated, 2 (16.6%) developed a UTI. Of the 29 patients with PVR between 200 and 350 ml in whom CIC was not initiated, 11 (37.9%) developed a UTI. Among the 143 patients with PVR <200 ml, 52 (36.3%) developed a UTI. The overall rate of UTI following onabotulinumtoxinA injection was 36% (67/189). The rate of UTI following onabotulinumtoxinA injection among patients in whom CIC was not initiated was 34.9% (65/186). No patients developed a febrile UTI.

Discussion

Intravesical onabotulinumtoxinA is a common therapy for bladder dysfunction in patients with neurological disorders and is now also widely used for the treatment of UUI and OAB. A possible complication of intravesical onabotulinumtoxinA injection is urinary retention. Previous trials have shown that higher doses of intravesical onabotulinumtoxinA are associated with higher rates of urinary retention and CIC; however, a review of the literature revealed a lack of consistent criteria for initiating CIC or actual rates of CIC initiation following intravesical onabotulinumtoxinA for the treatment of OAB. We identified 16 randomized trials evaluating the use of onabotulinumtoxinA for the treatment of OAB: three trials had no standardization regarding the initiation or cessation of catheterization, and one trial did not report the rate of CIC initiation at all [16]. The results of the remaining 12 trials are summarized in Table 3 [5–8, 13, 15, 17–21, 26]. Routine assessment of PVR was part of the protocol in all but one trial. In this trial, only women with symptoms of difficulty voiding were screened for retention, and CIC was initiated if PVR was 100–150 ml [19]. The rates of initiating CIC after intravesical onabotulinumtoxinA found in these trials was in the range 4.5–42.8% (Table 3).

CIC-related issues are the most common reason for patients to decline onabotulinumtoxinA as a treatment for OAB [15]. Despite this, the clinical consequences of asymptomatic elevated PVR after onabotulinumtoxinA injection are not well described, and it remains unclear if or when CIC should be initiated in these patients. For phase 3 clinical trials, strict guidelines were instituted regarding initiation of CIC. In a large number of these trials CIC was initiated based on an absolute PVR value, regardless of symptoms. As shown in Table 3, trials in which CIC was limited to symptomatic

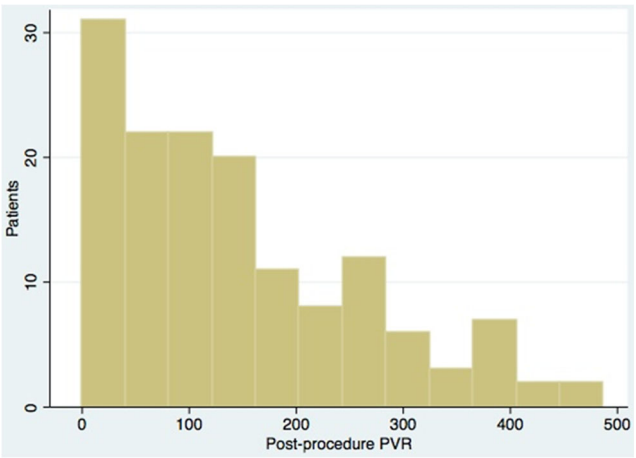

Fig. 1 Distribution of PVR volumes following injection of onabotulinumtoxinA

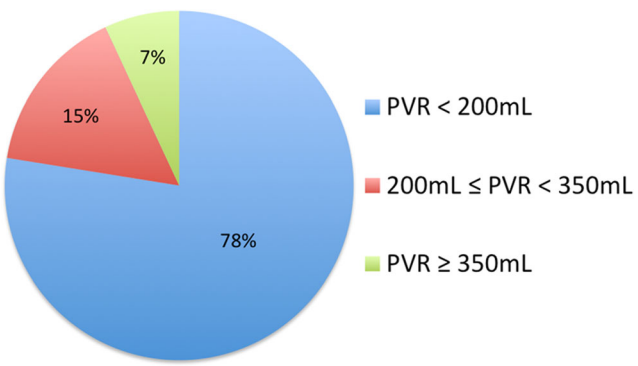

Fig. 2 Percentages of onabotulinumtoxinA injections following which the patient had an elevated PVR

Table 2 Rates of elevated PVR and CIC initiation following 187 onabotulinumtoxinA injections

	Number (%) of injections	Number (%) of patients with CIC
PVR <200 ml	143 (76.4%)	0 (0)
PVR 200–350 ml	29 (15.5%)	0 (0)
PVR >350 ml	13 (7.0%)	1 (0.5)
Acute retention	2 (1.0%)	2 (1.1)

patients showed lower rates of CIC than trials that included asymptomatic patients (4.5–15.5% vs. 13.6–42%). The results of our study indicate that symptoms, and not PVR alone, are an important determinant for initiating CIC after intravesical onabotulinumtoxinA injection. Furthermore, our study demonstrated that following onabotulinumtoxinA injection for the treatment of OAB, patients with asymptomatic elevation in PVR can be safely managed by observation only.

Numerous studies have qualitatively and qualitatively examined outcomes following initiation of CIC. Ease of use, convenience, discreetness, and psychological wellbeing are important to patients undergoing CIC [22]. Of patients undergoing long-term CIC, 20% perceive the technique as "not easy" or "not very easy" and 12% experience a decrease in quality of life, and 5% are unable or unwilling to master the technique [23, 24]. In addition to impacting quality of life, CIC is associated with development of symptomatic UTI in approximately 30–50% of patients and urethral bleeding in approximately 20% [24, 25]. Furthermore, rates of infection among women in whom CIC is initiated after onabotulinumtoxinA injection for OAB as high as 75–100% have been reported [5, 26]. It is therefore not surprising that patients decline intravesical onabotulinumtoxinA because of the risk of urinary retention.

In our study, we found that the true clinical rate of urinary retention, defined as inability to void or symptomatic PVR >350 ml, was only 1.6% compared with the reported rates of 4.5–42.8% in phase 3 clinical trials. More importantly, we demonstrated that asymptomatic women with an elevated PVR after onabotulinumtoxinA injection can be managed safely by observation without the risk of acute urinary retention or a subsequent elevation in PVR. Due to the small number of patients starting CIC, we were unable to determine if the incidence of UTI after treatment is lower if CIC is avoided. Although we attempted to examine the correlation between elevated PVR and UTI, this analysis was limited by the small sample size, and the fact that preprocedure antibiotic prophylaxis was not standardized during the entire study period. We recognize that the rate of postprocedure UTI in this study is significant, and we are currently investigating the impact of different antibiotic prophylaxis regimens on the rate of postprocedure UTI. Furthermore, our practice of routinely obtaining a postprocedure urine culture may make these rates not applicable to the general population.

As well as some strengths, including a relatively large population of female patients receiving a standardized dose of onabotulinumtoxinA with adequate follow-up, this study had some limitations mainly based on its retrospective nature. First, our series included patients with repeat injections, and we did not control for patients with repeat versus single injections in our analysis. However, we observed that the majority of

Table 3 Reported rates of CIC in randomized trials evaluating the use of onabotulinumtoxinA for idiopathic detrusor overactivity

Reference	Number of patients	Units injected	Criteria for initiating CIC	Number (%) of patients starting CIC
[6]	31	200–300	PVR >100 ml	6 (19.3)
[26]	16	200	PVR >150 ml	6 (37.5)
[5]	28	200	PVR >200 ml	12 (42.8)
[17]	22	100–200	PVR >200 ml	3 (13.6)
[18]	22	500	PVR >150 ml	4 (18)
[15]	100	200	PVR >150 ml	35 (35)
[19]	116	200	Symptoms + PVR 100–150 ml	18 (15.5)
[20]	15	100–200	PVR >200 ml with symptoms	1 (6.6)
[13]	44	100–150	PVR >100 ml with symptoms or PVR >200 ml	2 (4.5)
[21]	32	100–150	PVR >200 ml with symptoms	4 (12.5)
[8]	274	100	PVR >200 ml with symptoms or PVR >350 ml	19 (6.9)
[7]	278	100	PVR >200 ml with symptoms or PVR >350 ml	17 (6.1)

instances of elevated PVR occurred after the first injection and none occurred after the third injection. Second, although each patient received the same total dose of onabotulinumtoxinA, we did not standardize the injection technique, and it remains unknown if the number of injection sites affects the rate of urinary retention. Last, as mentioned above, our data regarding postprocedure UTI is limited by the lack of standardized preprocedure antibiotic prophylaxis.

Conclusions

In our series of 187 intravesical injections of 100 units of onabotulinumtoxinA for the treatment of OAB, the rate of postprocedure urinary retention requiring catheterization was only 1.6%. This low rate can be attributed to less rigorous criteria for CIC initiation than those applied in previous studies. While it remains important to counsel patients on the risk of retention after intravesical onabotulinumtoxinA injection, patients can be reassured that the actual rate of urinary retention requiring catheterization is low.

Compliance with ethical standards

Conflicts of interest None.

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