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Incomplete bladder emptying and urinary tract infections after botulinum toxin injection for overactive bladder: Multi-institutional collaboration from the SUFU research network

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Abstract

Introduction: Onabotulinumtoxin A (BTX-A) is an effective therapy for overactive bladder (OAB), however, adverse events may prevent patients from initiating therapy. The study objective was to report real-world rates of incomplete emptying and urinary tract infection (UTI) in men and women undergoing BTX-A for OAB.

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AUTHOR CONTRIBUTIONS

All authors listed qualify as authors, based on the following criteria: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

Approvals for the present study were obtained from each IRB at each clinical site.

Methods: Eleven clinical sites performed a retrospective study of adults undergoing first-time BTX-A injection (100 units) for idiopathic OAB in 2016. Exclusions included: postvoid residual (PVR) > 150 ml, prior BTX-A, pelvic radiation, or need for preprocedure catheterization. Primary outcomes at 6 months were incomplete emptying (clean intermittent catheterization [CIC] or PVR ≥ 300 ml without the need for CIC); and UTI (symptoms with either positive culture or urinalysis or empiric treatment). We compared rates of incomplete emptying and UTI within and between sexes, using univariate and multivariable models.

Results: 278 patients (48 men and 230 women) met inclusion criteria. Mean age was 65.5 years (range: 24–95). 35% of men and 17% of women had incomplete emptying. Men had 2.4 (95% CI: 1.04–5.49) higher odds of incomplete emptying than women. 17% of men and 23.5% of women had ≥1 UTI, the majority of which occurred within the first month following injection. The strongest predictor of UTI was a history of prior UTI (OR: 4.2 [95% CI: 1.7–10.3]).

Conclusions: In this multicenter retrospective study, rates of incomplete emptying and UTI were higher than many previously published studies. Men were at particular risk for incomplete emptying. Prior UTI was the primary risk factor for postprocedure UTI.

Keywords

complications; overactive bladder; retention; urinary tract infection

1 | INTRODUCTION

Idiopathic overactive bladder (OAB) is a common condition that affects one in seven US men and women and can be difficult to manage in some cases.[1] For individuals who cannot tolerate or fail medical therapy for OAB, onabotulinumtoxin A (BTX-A) is an effective third-line therapy to help control symptoms.[2] Multiple randomized controlled trials (RCTs) have demonstrated excellent efficacy of BTX-A injection in the treatment of idiopathic OAB.[3–5]

The primary adverse events associated with bladder BTX-A treatment are incomplete bladder emptying, particularly when bladder catheterization is warranted, and urinary tract infection (UTI). Published rates of clean intermittent catheterization (CIC) following BTX-A injection with 100 international units (the recommended starting dose for idiopathic OAB) range from 2% to 43%, often with lower rates reported in RCTs than in single-center, retrospective studies primarily including female patients.[6–8] The UTI rate in large RCTs has been reported as 15%–20%.[4,9]

Varying outcome measures between studies, such as different PVR thresholds to initiate CIC, can explain some of the variability in reported outcomes. Patient-level factors may also plan an important role. This is especially true given that *real-world* patients are not subjected to strict selection criteria inherent in RCTs. For instance, RCTs often exclude patients with recurrent UTIs. Generalizability of RCT data to the real-world patient population is limited given the strict inclusion criteria and also the general low predominance of men in RCT data.

Because of the wide range of published rates of incomplete bladder emptying and UTI, the aims of this study were to examine real-world rates of these outcomes in both men and women undergoing first-time BTX-A bladder injection with 100 units for idiopathic OAB and to identify potential risk factors for these important outcomes, through a multicenter research collaborative. We hypothesized that these outcomes would be higher in a patient sample more reflective of a *real-world* group than in a highly selected sample enrolled in an RCT.

2 | METHODS

We performed a retrospective study of men and women undergoing first-time bladder injection with 100 units of BTX-A for idiopathic OAB between January 1, 2016, and December 31, 2016. Eleven sites contributed cases for the study under the auspices of the SUFU Research Network, including Cedars Sinai Medical Center, Columbia University Irving Medical Center, Kaiser Permanente Los Angeles, University of Kansas, Lahey Clinic, NYU, University of Pennsylvania, University of California San Francisco (UCSF), University of Michigan, Vanderbilt University Medical Center, and Virginia Mason Medical Center. Internal Review Board approval was individually obtained by each data collection site.

2.1 | Study sample: Inclusion/exclusion

The target study sample was adult (age 18 and older) men and women undergoing first-time bladder BTX-A injection for idiopathic OAB with 100 units. A diagnosis of OAB was made by the treating physician, consistent with current AUA/SUFU guidelines.[2] Subjects were excluded if they had a concomitant diagnosis of a neurologic condition that may be associated with neurogenic bladder indication, including spinal cord injury, multiple sclerosis, or stroke; preprocedure postvoid residual >150 ml; preprocedure catheterization, including intermittent or indwelling; or history of pelvic radiation.

2.2 | Data collection

Data were abstracted from medical records by hand and entered into a REDCap database that was centrally housed at the SURN Data Coordinating Center (University of Michigan). Records were queried up to 6 months before and 12 months after the date of the index bladder BTX-A injection to collect data on baseline demographics, clinical characteristics, and outcome measures. Demographic and clinical data included: age, sex, race/ethnicity, height/weight or body mass index (BMI) (if already calculated), pre- or postmenopause status in women, conditions for the Functional Comorbidity Index, and prior history of recurrent UTI (two or more within 6 months).[10,11] Prior OAB treatment (pharmacologic and nonsurgical therapy) and GU surgeries were also recorded, as well as the three most recent PVR assessments before index procedure, if available. The mean of up to three PVR values was calculated and used for the pre-BTX-A PVR. Periprocedural data included: setting (OR or clinic); anesthetic type (general, sedation, local); peri- or postprocedural antibiotics; and urinalysis. Following the index procedure, data were abstracted from each postprocedure visit in the 6 months following the index procedure, including the visit date, PVR (ml), whether catheterization was required, and whether UTI was present. If a UTI was

noted, data was collected including which antibiotics were prescribed and how the UTI was diagnosed (e.g., urinalysis, urine culture, or symptoms). Retreatment for BTX-A within 12 months was also recorded.

2.3 | Outcomes

We had two primary outcomes: incomplete bladder emptying and UTI. We defined incomplete bladder emptying primarily as the need for catheterization or a postprocedure PVR ≥ 300 ml without the need for catheterization at any time during the 6 months after BTX-A injection, consistent with prior definitions in the literature.[6,11] Secondary outcomes included evaluation of patients with a postprocedure PVR (separated into tertiles of <200 L, 200–299 ml, and ≥ 300 ml), the number of patients in whom catheterization was initiated for each PVR category, and the number of UTIs per subject in the 6 month follow-up period.

We defined UTI by diagnosis by the treating provider, including whether antibiotics were initiated for presumed UTI, positive culture or UA, and symptoms.

2.4 | Statistical analyses

The population of patients who underwent BTX-A bladder injection were described in total and by sex with descriptive statistics. Comparisons were made with t tests or Wilcoxon rank tests for continuous variables and appropriate χ^2 square tests for categorical variables. The primary outcomes (incomplete emptying and UTI) and the components of incomplete emptying, catheter, and PVR, were compared between sexes. Logistic models were used to assess associations with each primary outcome separately including our primary exposure variables, age, sex, race, BMI, comorbidities, pre-BTX-A PVR, procedure setting, number of injections, and history of UTI. Univariate and multivariable models were reported. Data analyses were completed using SAS 9.4 (SAS Institute) with statistical significance assessed with a 5% Type I error.

3 | RESULTS

There were 401 entries into the RedCap database. Five represented duplications, 62 did not meet inclusion criteria, and 56 did not have complete follow-up data. This resulted in 278 patients (48 men and 230 women) who underwent BTX-A bladder injection with 100 units for idiopathic OAB between January 1 and December 31, 2016, with complete data. Demographic and background clinical data for these patients are present in Table 1. There was no statistical difference in baseline demographic data between male and female subjects.

Overall, 56 (20%) male and female subjects met our definition for incomplete emptying (either started CIC or had a PVR≥ 300 ml) within 6 months after initial BTX-A bladder injection. This was more common in men (35.4%) than in women (17.0%, $p = 0.004$). Specific data on rates of PVR and CIC are presented in Table 2. UTI was diagnosed in 62 (22%) of subjects and did not differ significantly between men (16.7%) and women (23.5%, $p = 0.30$). Of the 54 women with UTI, 13 experienced 2 or more UTIs in the 6-month follow-up period, while in men, only 2 had more than one UTI (Table 2).

Only sex was predictive of incomplete bladder emptying in our multivariate models (Table 3). Men had an increased odds of retention compared to women (adjusted odds ratio [aOR]: 2.40, 95% CI: 1.04–5.49). However, none of the other predictor variables remained significant in the model. For UTI, a prior history of UTI was significantly associated with a higher odds of a postprocedure UTI (aOR: 4.20, 95% CI: 1.72–10.27). (Table 4). None of the other predictor variables were associated with odds of developing UTI.

4 | DISCUSSION

In this multicenter, retrospective study we find that one in five participants develop incomplete bladder emptying and UTI within 6 months following 100 U intravesical BTX-A injection. Our study finds that the odds of incomplete emptying are 2.4 times greater for men compared to women. We also find that 22% of patients experienced UTI following intravesical BTX-A injection. Patients who had a prior history of UTI had significantly greater odds of developing UTI following BTX-A injection. These data provide pragmatic information to help patients and clinicians decide whether the benefits of 100 units of BTX-A for OAB outweigh the risks.

The published rates of incomplete bladder emptying after 100 units BTX-A injection varies widely from 1% to 48.9%[4,6–8,11,12] (Table 5). RCTs tend to report lower rates ranging from 5% to 20%, while observational and cohort studies that are dominated by single institutions, tend to report higher rates, up to 48.9%.[4,6–8,11,12] (Table 5) Manufacturer prescribing information reports that 6% of patients who undergo 100 units intravesical BTX-A injection require catheterization and that 3% experienced incomplete bladder emptying without requiring catheterization among nondiabetic patients.[13] In the present study, the overall rate of incomplete emptying among men and women was much higher.

Prior studies have found that specific populations may be at higher risk for urinary retention.[12–14] Faure Walker and colleagues noted a de-novo CIC rate of 42.6% in men and 35.3% in women after 100 units.[12] In a study of women undergoing 100 units found that older age and history of three or more vaginal deliveries were associated with requiring de-novo CIC.[14] Patients with diabetes mellitus have also been found to have nearly double the rates of urinary retention, however, this finding is not consistent across studies.[13,14] Similar to these previous reports, we find that men have higher odds of developing urinary retention compared to women, however, we do not find that age or comorbidities to be associated with retention.

Prior studies report rates of UTI after BTX-A injections of 16%–44%.[3,4,6–8,11](Table 5). Prescribing information cites rates of between 18% and 31%.[13] The rate in the present study (22%) is consistent with these results. While prior studies suggest that diabetes and incomplete emptying and comorbidities are risk factors for UTI following BTX-A, our study did not corroborate these findings. In the present study, the biggest predictor of whether a patient will have UTI following BTX-A is whether they have a history of UTI.

As noted, there is little standardization of outcome measure definitions. Our definition of incomplete bladder emptying (i.e., the need for catheterization or a postprocedure PVR ≥

300 ml without catheterization at any time during the 6 months after BTX-A injection) is consistent with prior studies.[4,7,12] Most RCTs investigating BTX-A required catheterization if postprocedure PVR reached certain thresholds, even in the absence of symptoms (Table 5). Pivotal BTX-A studies used a maximum PVR = 350 ml to initiate catheterization.[8] As shown in Table 2, if lower PVR values were used, as in other studies, our rates of incomplete bladder emptying would be even higher (e.g., 31% if PVR of 200 ml used).[4] In the current study, using a higher cut-off value for PVR (i.e., 350 ml) did not change the findings.

We also opted for a broad definition of UTI, defined as a UTI diagnosed by the treating provider, whether antibiotics were initiated for presumed UTI, there was a positive culture or UA, and the subject had symptoms of UTI. Our rationale for this pragmatic approach was that this would better allow us to capture this outcome retrospectively, as we anticipated that specific data from urine laboratory analyses or culture results would be difficult to document. Even though this broad definition may overestimate rates of UTI after BTX-A therapy, our rates of UTI in this study were consistent with those reported by prior studies.

There are several limitations to consider in interpreting the study findings. Primarily, this was a retrospective study, subject to many limitations inherent in the study design. Data were manually abstracted from electronic medical records and thus subject to information bias and errors in entry. Because data were only available for follow-up visits occurring at a specific clinical site, additional data resulting from patient visits to other sites (e.g., primary care or urgent/emergency room) may not have been available for inclusion. This may have resulted in undercounting of certain outcomes. In addition, patient selection, BTX-A delivery, and identification and management of adverse events were not standardized across study sites and likely varied by site, reflecting individual provider and practice preferences. Multichannel urodynamics were also not a selection criterion for the present study, reflecting prior BTX-A studies, clinical guidelines, and differences in practice preferences, so we were not able to analyze the role these findings may have had on our primary outcomes. Because outcome measures were not standardized, we were unable to report on efficacy outcomes following BTX-A treatment, so we do not know whether our patients had higher or lower rates of clinical success than expected.

Despite these limitations, there are several strengths to the study to note as well. Collecting data from multiple clinical sites representing high-volume BTX-A practices helps to generalize our findings to the wider OAB population. Unlike prior studies, we intentionally included male patients to make direct comparisons of outcomes by sex, which is a unique approach to examining outcomes following BTX-A for OAB. More specifically, 17% of our study subjects were male, which is higher than the proportion reported in most RCTs. Finally, our relatively unselected study sample that was not subject to strict inclusion criteria, such as those inherent to an RCT, more likely reflects a “real-world” experience in treating men and women with OAB.

5 | CONCLUSION

In this multicenter, retrospective study of 278 consecutive men and women undergoing first-time, 100 U BTX-A injections for idiopathic OAB, the rates of incomplete bladder emptying

and UTI in the 6 months following treatment were 18% and 22%, respectively. Male sex and prior UTIs were the primary factors identified that predicted incomplete emptying and UTI, respectively. While these outcomes are higher than many previous reports, the nonselective nature of the study suggests the findings may reflect outcomes experienced in “real-life” patient care.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TABLE 1

Baseline demographics of study cohort by sex

Variable	Total	Men	Women	*p* value
N	278	48	230	
Age, mean (SD) (range)	65.5 (14.3) (23.7–95)	68.4 (14.8) (24.7–87)	64.9 (14.1) (23.7–95)	0.12 (*t* test)
Race/ethnicity				0.39 (FE)
Non-Hispanic White	201 (72.3)	32 (66.7)	169 (73.5)	
Non-Hispanic Black	24 (8.6)	5 (10.4)	19 (8.3)	
Hispanic	30 (10.8)	7 (14.6)	23 (10.0)	
Other/unknown	23 (8.3)	4 (8.3)	19 (8.3)	
BMI, mean (SD) (range)	30.7 (7.9) (15.9–62.5)	29.6 (6.2) (22.3–51.3)	30.9 (8.2) (15.9–62.5)	0.22 (*t* test)
Normal	65 (26.5)	10 (24.4)	55 (27.0)	0.43 (JT)
Overweight	64 (26.1)	14 (34.2)	50 (24.5)	
Obese	57 (23.3)	11 (26.8)	46 (22.6)	
Morbid obesity	59 (24.1)	6 (14.6)	53 (26.0)	
Comorbidity index				0.18 (MH)
0–2	32 (11.5)	10 (20.8)	22 (9.6)	
3–4	168 (60.4)	24 (50.0)	144 (62.6)	
5–6	78 (28.1)	14 (29.2)	64 (27.8)	
Postmenopausal		n/a	167 (87.0)	
History of UTI	36 (13.0)	5 (10.4)	31 (13.5)	0.57 (FE)
Pre-BTX-A PVR, median, (min–max); mean (SD)	14 (0–150)	3.5 (0–150)	16.5 (0–150)	0.23 (Wilcox)
	27.7 (35.9)	27.0 (40.1)	27.9 (35.0)	
0–75 ml	247 (88.8)	43 (89.6)	204 (88.7)	0.86 (CS)
76–150 ml	31 (11.2)	5 (10.4)	26 (11.3)	
Procedure setting				0.56 (CS)
Clinic	161 (57.9)	26 (54.2)	135 (58.7)	
Operating room	117 (42.1)	22 (45.8)	95 (41.3)	
Number of injections				0.43 (CS)
5–10	126 (49.2)	23 (54.8)	103 (48.1)	
11–30	130 (50.8)	19(45.2)	111 (51.9)	

Abbreviations: CS, χ^2 test; FE, Fisher's exact test; JT, Jonckheere–Terpstra test; MH, Mantel–Haenszel $\chi 2$; Wilcox, Wilcoxon Rank test.

TABLE 2

Outcomes for urinary retention and urinary tract infection among men and women in the 6 months following injection with onabotulinumtoxin A

Outcome	Men, *N* = 48	Women, *N* = 230	*p* value
Urinary retention			
Started CIC within 6 months	13 (27.1)	32 (13.9)	0.02
Postvoid residual			
Mean (SD)	162.4 (156.9)	125.8 (127.4)	0.34
Median (range)	119.5 (0–500)	82 (0–530)	
PVR value, *N*(%)			
<200 ml	27 (61.4)	155 (75.6)	0.04
200–299 ml	6 (13.6)	25 (12.2)	
≥300 ml	11 (25.0)	25 (12.2)	
Started CIC at the following PVR			0.72
<200 ml	1 (8.3)	6 (18.8)	
200–299 ml	4 (33.3)	8 (25.0)	
≥300 ml	7 (52.3)	18 (56.3)	
Total retention rate (started CIC or PVR ≥ 300 ml)	17 (35.4)	39 (17.0)	0.004
Urinary tract infection (UTI)			
≥1 UTI within 6 months	8 (16.7)	54 (23.5)	0.30
Number of UTIs per subject within 6 months			
0	40 (83.3)	176 (76.5)	0.30
1	6 (12.5)	41 (17.8)	
2	2 (4.2)	7 (3.0)	
3	0	5 (2.2)	
4	0	1 (0.4)	

Abbreviations: CIC, clean intermittent catheterization; PVR, postvoid residual; UTI, urinary tract infection.

TABLE 3

Odds of developing urinary retention within 6 months of injection with Onabotulinumtoxin A

		Univariate model			Multivariate model		
Variable	**Observations (# with retention/*N*)**	**Odds ratio**	**95% CI**	***p* value**	**Odds Ratio**	**95% CI**	***p* value**
Age	56/278	1.02	0.99–1.04	0.17	1.00	0.98–1.03	0.82
Gender							
Female	39/230	Ref	-	0.0047	Ref	-	0.04
Male	17/48	2.69	1.36–5.33		2.40	1.04–5.49	
Race/ethnicity							
Non-Hispanic White	45/201	Ref	-	0.35	Ref	-	0.09
Non-Hispanic Black	3/24	0.50	0.14–1.74		0.24	0.29–1.98	
Hispanic	3/30	0.39	0.11–1.33		0.17	0.034–0.80	
Other/unknown	5/23	0.96	0.34		0.82	0.22–3.05	
BMI	51/245	0.96	0.92–1.00	0.06	0.97	0.92–1.0	0.18
Comorbidity Index							
0–2	12/32	Ref	-	0.10		-	0.37
3–4	31/168	1.11	0.35–3.50		0.52	0.21–1.29	
5–6	13/78	0.56	0.19–1.67		0.68	0.20–2.27	
Pre-BTX-A PVR, median							
0–75 ml	49/247	Ref	-	0.72	Ref	-	0.84
76–150 ml	7/31	1.18	0.48–2.89		1.12	0.39–3.25	
Procedure setting							
Clinic	38/161	Ref	-	0.09	Ref	-	0.16
Operating room	18/117	0.59	0.32–1.09		0.59	0.29–1.24	
Number of injections							
4–10	33/126	Ref	-	0.03	Ref	-	0.10
11–20	20/130	0.51	0.74–3.09		0.55	0.27–1.12	
History of UTI							
No	47/242	Ref	-	0.44	Ref	-	0.18
Yes	9/36	1.38	0.61–3.14		2.01	0.72–5.57	

Abbreviation: PVR, postvoid residual.

TABLE 4

Odds of developing a urinary tract infection within 6 months of injection with onabotulinumtoxin A

		Univariate model			Multivariate model		
Variable	**Observations (# with retention/*N*)**	**Odds ratio**	**95% CI**	***p* value**	**Odds ratio**	**95% CI**	***p* value**
Age	62/278	1.01	0.99–1.03	0.30	1.01	0.98–1.03	0.62
Gender							
Female	54/230	Ref	-	0.31	Ref	-	0.35
Male	8/48	0.65	0.29–1.48		0.65	0.26–1.62	
Race/ethnicity							
Non-Hispanic White	49/201	Ref	-	0.41	Ref	-	0.16
Non-Hispanic Black	3/24	0.44	0.13–1.55		0.60	0.16–2.31	
Hispanic	7/30	0.94	0.38–2.33		0.46	0.15–1.44	
Other/unknown	3/23	0.47	0.13–1.63		0.13	0.02–1.17	
BMI	58/245	1.02	0.99–1.06	0.26	1.04	1.00–1.08	0.07
Comorbidity Index							
0–2	10/32	Ref	-	0.11		-	0.30
3–4	40/168	0.40	0.14–1.16		0.61	0.24–1.55	
5–6	12/78	0.35	0.12–0.93		0.40	0.12–1.27	
Pre-BTX-A PVR, median							
0–75 ml	53/247	Ref	-	0.34	Ref	-	0.55
76–150 ml	9/31	1.50	0.65–3.45		1.33	0.52–3.39	
Procedure setting							
Clinic	39/161	Ref	-	0.37	Ref	-	0.07
Operating room	23/117	0.77	0.43–1.37		0.54	0.27–1.06	
History of UTI							
No	45/242	Ref	-	0.0002			0.0017
Yes	17/36	3.92	1.89–8.13		4.20	1.72–10.27	

Abbreviation: PVR, postvoid residual.

TABLE 5

Summary of UTI and Incomplete Emptying rates reported in prior studies of intradetrusor onabotulinumtoxina

Study	Design	Units	Inclusion/exclusion	Incomplete empty definition	IE rate	UTI definition	UTI rate
Brubaker (2008)	RCT	200 units BTA	PVR < 150 ml or SIC	PVR ≥ 200 ml	43%		44%
Dmochowski (2010) [5]	RCT	Dose ranging: 50–300 units	PVR < 200 ml 8+ UUI per week and ave 8+ voids per day	PVR > ≥ 200	18% 11% SIC		36%
Visco (2012) [7]	RCT	100 units	PVR < 150 ml 5+ UUI in 5 days	PVR ≥ 150 with symptoms; or PVR ≥ 300	Do not give overall #	Not Reported	33%
Nitti (2013) [9]	RCT	100 units	PVR < 100 ml 3+ UUI in 3 days and ave 8 voids per day	PVR ≥ 200 with symptoms; or PVR ≥ 350 Retention = PVR ≥ 200 requiring SIC	I.E. = 5.4%; SIC = 6.1%	Positive urine culture	15.5%
Amundsen (2016) [12]	RCT	200 units	PVR < 150 ml 6+ UUI in 3 days	PVR ≥ 200 with symptoms; or PVR ≥ 300	20% at any visit	Not Reported	35%
Rahnama'i (2017)[15]	Retrospective series	Up to 300 Units	Included NGB		De novo CIC rate 24%		
Moita (2017)[14]	Prospective cohort	100 Units	Women with idiopathic OAB		Retention requiring ISC 6% at 2 weeks, 0 at 12 weeks.; PVR > 200 6% @ 2 weeks, 0.4% at 12 weeks	Not Reported	Not Reported
Patel (2018)[8]	Retrospective series	100 units	Any women undergoing BTX-A injection with ROAB, no PVR limits	<200 200–349 ≥350	1% @ 2 weeks	+UCx with symptoms	36%
Faure Walker (2019)[13]	Retrospective series	Up to 300 units	Men and women		48.9% de novo CIC in men receiving 100 U; 35.3% in women receiving up to 300 U		

Abbreviations: CIC, clean intermittent catheterization; PVR, postvoid residual; RCT, randomized controlled trial; UTI, urinary tract infection; UUI, urgency urinary incontinence epsidodes.