The intravesical injection of highly purified botulinum toxin for the treatment of neurogenic detrusor overactivity

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Abstract

Introduction: We aimed to assess safety and efficacy of incobotulinumtoxinA for the treatment of neurogenic detrusor overactivity (DO).
Methods: We identified patients with neurogenic DO confirmed on urodynamics (UDS) and reported urgency incontinence (UI) in those who received intravesical incobotulinumtoxin A injection for neurogenic bladder between November 2013 and May 2017. Parameters studied were daytime frequency, daily incontinence episodes, daily pad use, clean intermittent catheterization (CIC) volumes, symptom scores (UDI6, IIQ7, PGII), and complications.
Results: We examined 17 male patients who met inclusion criteria and underwent incobotulinumtoxinA injection. Mean age was 61.2±15.4 years. Fourteen patients (82%) were taking oral antimuscarinics prior to the incobotulinumtoxin A injection. There were improvements in the following parameters: average daily pads (4.5 to 3.3, p=0.465), daily urinary frequency (9.4 to 4.6, p=0.048), daily incontinent episodes (2.5 to 0.4, p=0.033), CIC volumes (400 to 550 mL, p=0.356), hours in between CIC (3.6 to 5.2, p=0.127), and the validated questionnaires UDI6 (30.6 to 7.4, p=0.543) and IIQ7 (52.4 to 6.8, p=0.029). There were no documented symptomatic urinary tract infections (UTIs) within 30 days of injection or reports of de novo urinary retention. Nine of 17 patients (53%) reported being dry at their first postoperative visit.
Conclusions: In this preliminary pilot study of a small cohort of males with neurogenic DO and UI, significant improvements were seen following incobotulinumtoxinA injection in daily frequency, incontinence episodes, hours in between CIC, and quality of

life. Larger-scale and long-term studies are required to confirm these results, but initial findings are promising for wider use of this formulation.

Introduction

Intradetrusor injection of botulinum toxin type A is an effective treatment for overactive bladder (OAB) and neurogenic detrusor overactivity (NDO)[1]. Botulinum toxin A is one of seven serotypes of toxins produced by Clostridium botulinum. There are several commercial forms of botulinum toxin A, all with similar toxin structures, but with slightly different protein modifications[2]. One commercial form of botulinumtoxinA, onabotulinumtoxin A or Botox®, is FDA approved for urinary incontinence (UI) and overactive bladder (OAB) symptoms[3]. Multiple pivotal studies have shown the effectiveness of onabotulinumtoxinA in idiopathic overactive bladder syndrome (OAB)[4, 5]. In patients with NDO, multiple trials have also demonstrated effectiveness of onabotulinumtoxinA for urinary incontinence. In a phase III, double-blind, randomized, multicenter placebo controlled trial by Ginsberg et al, 416 patients with spinal cord injuries or multiple sclerosis were randomized to either onabotulinumtoxinA or placebo[6]. OnabotulinumtoxinA significantly reduced UI episodes/week and improved urodynamic parameters and quality of life compared to placebo in patients with NDO[6]. In an extension study benefit was still seen at 4 years with repeat treatments as needed[7]AbobotulinumtoxinA (Dysport®) and rimabotulinumtoxinB (NeuroBloc®) are other neurotoxin forms available in the U.S. that have been studied for use in the bladder. In a prospective study of 207 patients with idiopathic OAB by Ravindra et al, abobotulinumtoxinA was found to be inferior to onabotulinumtoxinA for the treatment of idiopathic OAB as it had twice the rate of symptomatic urinary retention requiring CIC[8]. It was shown these toxins were not interchangeable at equal doses[8]. Peyronnet et al. reported on the efficacy and safety of intradetrusor injection of abobotulinum toxin A 750U in patients with neurogenic DO[9]. The success rate, which was a composite parameter including continence, number of catheterizations, and lack of DO, was 64.2. In 2007, Hirst et al. studied the effect of intradetrusor rimabotulinumtoxinB in a non-randomized study including 25 patients with both idiopathic and neurogenic detrusor activity (5 with NDO due to transverse myelitis and multiple sclerosis). Subjective improvements were seen in a small portion of the idiopathic detrusor activity patients, with two NDO patients reporting no improvement[10]. This study showed a short duration of action of rimabotulinumtoxinB, with effects wearing off by 10 weeks in most of their patients[10].

IncobotulinumtoxinA, commercially known as Xeomin® (Merz Pharmaceuticals GmbH, Frankfurt, Germany), is another commercially available form of botulinumtoxinA

and was approved by the FDA in 2011 for cervical dystonia and blepharospasm[11]. It is a highly purified form of this toxin with no complexing proteins[11]. It has been postulated that given its purity, there is less immunogenicity in patients. Potentially decreased immunogenicity of this botulinumtoxinA may be particularly advantageous in the neurogenic population, who often receive injections in multiple different organs. However, it is unclear if the differences in immunogenicity are clinically relevant in this setting. There are no maximum dosing ranges published by the manufacturer for the intravesical administration of incobotulinumtoxin. For limb spasticity incobotulinum toxin has shown to be as effective as ONA with a comparable adverse event profile when a clinical conversion ratio of 1:1 was used[12]. In limb spasticity, dosage of up to 800U have been used without compromising safety or tolerability[13].

In contrast to onabotulinum toxin, incobotulinumtoxin can be stored at room temperature for ≤ 36 months before reconstitution. There is also evidence that equal product efficacy with 25ºC storage (room temperature) can be maintained 1 week post reconstitution[14]. IncobotulinumtoxinA and onabotulinutoxinaA were found to have comparable effects on DO and similar adverse event profiles with an almost 1:1 conversion ratio[15 16]. Most studies on NDO outcomes have involved Dysport® and Botox®[17]. Dosing differences and interchangeability between toxin types in terms of clinical impact remains an important area of future research[17].

Additionally, incobotulinumtoxinA is generally less expensive than onabotulinumtoxinA, making this an attractive and more cost-friendly alternative for OAB patients with UI. Tilden et al showed that incobotulinumtoxinA was more cost effective, compared to onabotulinumtoxinA in patients with blepharospasm and cervical dystonia in the Australian health care system[18]. They found an incremental cost/quality-adjusted life-year gained of $25,588 in incobotulinumtoxinA and $23,794 in onabotulinumtoxinA[18]. The effectiveness of this more purified, less immunogenic incobotulinumtoxinA for neurogenic DO with UI has not yet been well studied.

In 2015, incobotulinumtoxinA was approved in the U.S. for upper limb spasticity in adults. Other non-FDA indications include chronic sialorrhea and temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity[19]. Some benefits of incobotulinumtoxinA versus placebo for upper limb spasticity were shown in the post-stroke population by Kanovsky et al in a prospective, non-randomized study of 148 people, completed in 23 European sites[20]. IncobotulinumtoxinA injections resulted in significant and sustained improvements in muscle tone and disability in this patient population[20].

To date, this formulation has not yet been well studied for use in the bladder. In a study by Conte et al., the objective was to investigate whether bladder dysfunction in MS patients depends on suprapontine or spinal lesions. 25 MS patients who were spontaneously voiding and had low PVRs underwent intradetrusor injection with 100U

incobotulinumtoxinA.[21]. No significant differences were seen in the Hoffman reflex after injection. However, there were improvements in volumes at first, normal, strong desire, dyssynergic activity, and voiding diary parameters[21].

The primary objective of this study was to assess the safety and effectiveness of incobotulinumtoxinA in patients with neurogenic DO and UI.

Methods

Study design and participants

After Institutional Review Board (IRB) approval, patients were identified in a retrospective manner at a single Veteran's Affairs Medical Center (VAMC) with neurogenic bladder who had undergone intradetrusor incobotulinumtoxinA injections between November 2013 and May 2017. All patients had previously failed antimuscarinic therapy and had neurogenic DO and UI. There was no strict definition utilized to define antimuscarinic failure. It was assumed that patients who had persistent bothersome voiding symptoms while on the medical therapy were refractory.
All patients underwent detailed history, physical examination, urinalysis, urine culture, and video urodynamics (UDS) prior to injection.

Video UDS were done according to International Continence Society (ICS) standards with fluid filled system and external transducers at the reference level of the upper edge of the symphysis pubis using Medtronic® UDS equipment[22]. The baseline bladder capacities of all patients were determined from the most recent UDS preceding the first injection of incobotulinumtoxinA.

Patients with injections of onabotulinumtoxinA within 1 year of incobotulinumtoxinA treatment were excluded. Of note, patients with prior onabotulinumtoxinA injections were receiving incobotulinumtoxinA due to the new hospital standard of administering this less expensive formulation. However, there was varying levels of efficacy and satisfaction with the onabotulinumtoxinA among the patients. We recorded demographic patient information and baseline clinical data. Additionally, the patients were assessed for average voiding parameters at home, including daily pad use, frequency, incontinence episodes, and CIC volumes. Patient responses to the following validated questionnaires were also recorded: Incontinence Impact Questionnaire (IIQ-7), Urogenital Distress Inventory (UDI-6), and Patient Global Improvement of Incontinence (PGI-I). The averages of the IIQ-7 and UDI-6 surveys were converted to a 100-point scale. While there are no globally accepted cutoffs, higher scores on the 100 point scale represent higher impact and distress scores[23]. Patients returned for a follow-up visit within 2-4 weeks following the incobotulinumtoxinA injection and all patients were evaluated. Complications within 30 days of incobotulinumtoxinA injection and de novo urinary retention were recorded.

Statistical analyses

Chi-squared and Fisher's Exact test was used for categorical variables and the Mann-Whitney U test for continuous variables. All data analyses were done using IBM SPSS software, Version 23 (IBM Corporation, Armonk, NY). Multivariate analysis was attempted, but limited due to the small sample size. Statistical analysis was done with SPSS Statistics 23.0.

Procedure technique

Patients with positive urine cultures were treated with appropriate antibiotics prior to injection. Patients were placed in the dorsal lithotomy position and administered either local anesthesia or conscious sedation, depending on patient anxiety level and/or history of autonomic dysreflexia from other local procedures. Incobotulinum toxin was diluted in normal saline, with 200U diluted in 20 mL and 300U diluted in 30 mL. Given this was a retrospective study with a heterogeneous group of urologists; the amount of incobotulinumtoxin administered was at the discretion of the respective providers. A rigid cystoscope was inserted through the urethra under direct vision and 1mL injections were distributed throughout the bladder wall including at the trigone.

Results

Patient demographics and baseline characteristics

A total of 17 participants with neurogenic DO (confirmed on UDS) and refractory UI were included in this study. All participants were male with mean age of 61.2 ± 15.4 years. Prior to incobotulinumtoxin injection, six (35%) patients had indwelling Foley, six (35%) were voiding on their own, and five (30%) were doing CIC. Eleven patients had SCI: four thoracic spine injuries and seven cervical spinal cord injuries. One patient had a primary diagnosis of multiple sclerosis (MS) with a history of stroke. Two patients had diagnoses of Parkinson's disease (one with a concurrent thoracic SCI) and four had a history of stroke (with one also having MS). 5 (29%) patients overall had a concurrent diagnosis of severe traumatic brain injury (TBI).

Two (12%) patients had diabetes mellitus (DM) and 3 (18%) patients had a history of chronic kidney disease (CKD). Table 1 summarizes baseline characteristics of the participants. Comorbidities were captured with the Charlson Age Comorbidity indexes, reported in Table 1. In terms of previous conservative management, 82% of the participants had been using oral antimuscarinics regularly for at least one month prior to their first incobotulinumtoxinA injection.

Eight (47%) participants had undergone previous injections with onobotulinumtoxinA. (greater than one year before incobotulinumtoxinA injection). Nine (53%) patients had repeat injections of incobotulinumtoxinA after their initial injection in

the study period. Seven (41%) participants had injections with 300 units and ten patients (59%) received 200 units.

Overall, 100% of patients underwent repeat intradetrusor incobotulinum toxin within 1 year of the initial procedure. Median time to first repeat injection was _34 weeks (IQR 29-64). 24% of patients underwent more than one repeat injection within 1 year of the initial study injection.

Clinical outcomes

Postoperative data was obtained from two weeks to one month after the patients' first incobotulinumtoxinA injection. Table 2 illustrates outcomes following incobotulinumtoxinA injection in patients who were already on a CIC regimen. Following treatment, the median for daily pads was stable at 0. The median number of incontinent episodes decreased from 2 to 0 after treatment. Median volumes with CIC improved, 400 to 550, as well as median number of hours between CIC, 4 to 6 pre and post-treatment. Average scores for the UDI6 and IIQ7 surveys also improved pre and post-treatment, respectively. All patients in this group were dry following their initial injection, with no one requiring pads after treatment.

Table 3 outlines similar outcomes in patients who were voiding prior to this study. Following treatment, the median for daily pads was 12 from 7.5. The median number of incontinent episodes decreased from 2.5 to 1 after treatment. Average scores for the UDI6 and IIQ7 surveys also improved pre and post-treatment, respectively. Two patients versus none were dry after treatment. All patients in this group were dry following their initial injection, with no one requiring pads after treatment.

Finally, Table 4 summarizes results for the subgroup with chronic Foley catheters and SP tubes. Creatinine levels remained stable over time. Average IIQ7 and UDI-6 survey scores were also markedly improved in this group. All patients were dry after an initial course of treatment.

Ten participants overall completed PGI-I surveys postoperatively and results are shown in Figure 1. In the non-voiding group, three participants completed the survey. One participant each (33%) endorsed feeling a little better, much better, and very much better, totaling ~33% for each response. In the voiding group, four participants (66.6%) endorsed feeling very much better after their initial incobotulinumtoxinA injection. One participant each (16.7%) endorsed feeling a little better and much better. Of note, no participants reported no improvement or feeling worse after treatment. Nine of the seventeen patients (53%) reported being dry at their first postoperative visit. One patient who initially had an indwelling Foley prior to incobotulinumtoxinA treatment was able to successfully initiate and perform CIC following intravesical treatment. This was a patient with bilateral Grade 4 vesicoureteral reflux and a small bladder capacity of about 215mL on UDS. Of note, this patient had resolution of hydronephrosis on renal ultrasound following intravesical treatment with incobotulinumtoxin.

No patients had documented symptomatic urinary tract infections (UTIs) or other adverse effects in the 30 days following treatment.

Discussion

In this cohort of patients with neurogenic bladder and DO there were clinically significant improvements in frequency and daily incontinent episodes after an initial injection with incobotulinumtoxinA. Additionally, in patients doing CIC, significant improvements were seen in time between catheterization. Furthermore significant improvements were seen in quality of life scores. All patients, whether voiding or not, reported global impression of improvement following treatment. The initial results of this pilot study provide promising evidence that incobotulinumtoxin A can be a reasonable alternative to onabotulinumtoxin A in patients with UI and other OAB symptoms.

To our knowledge, this is the first study of its kind to examine the effects of incobotulinumtoxinA on bladder diary, urodynamic parameters and quality of life measures in a range of patients with NDO, both voiding and not voiding. Only one other study has examined the effect of intradetrusor injection of incobotulinumtoxinA. Conte et al. completed a study investigating the neurophysiological effects of 100 U incobotulinumtoxinA in patients with neurogenic DO due to multiple sclerosis who were spontaneously voiding with low post-void residual[21]. The primary aim of the study was to investigate whether in MS bladder dysfunction is due to suprapontine or spinal lesions, by examining change in the soleus Hoffman reflex. This study showed improvements in first, normal, and strong desire during UDS, with no change in the Hoffman reflex[21]. This population of neurogenic bladder patients was very different than our patient population, comprised mostly of SCI patients of which only 35% were voiding spontaneously. Furthermore, the dosage of medication used was different.

Our results are very similar to those observed in patients with neurogenic DO who have undergone intradetrusor injection of onabotulinumtoxinA. Cruz et al. randomized patients with MS (n-154) or SCI (n=121) to placebo, 200U onabotulinumtoxinA, of 300U onabotulinumtoxin A. At week 6, significant improvements were seen compared to placebo in incontinence episodes per week, urodynamics parameters and quality of life.

This is the first paper to look at voiding parameters after any botulinumtoxin formulation in the bladder of TBI patients, despite neurogenic bladders being common sequelae of TBI. Prior literature has studied outcomes of botulinum toxin A injection in these patients but in upper and lower limb spasticities. Fock et al did a prospective, non-randomized study in seven patients with a history of TBI secondary to motor vehicle trauma and suffering from spastic equinus[24]. Patients were injected with onabotulinumtoxin A into the heads of the gastrocnemius and soleus muscles only, totaling 300u, and six of the seven patients showed significant improvements in walking speed and stride length at 12 weeks [24]. In this study significant improvements were seen

in quality of life following intradetrusor injection of incobotulinumtoxinA. 90% of patients who completed the PGI-I postoperatively noted some degree of improvement within the month after their injections. These findings are in keeping with other studies examining the effects of intradetrusor injection of botulinum toxin. Ginsberg et al showed a significant improvement in impact on quality of life in neurogenic bladder patients, which was not impacted by the initiation of CIC[6]. Similarly, Nitti et al showed that in idiopathic OAB patients there were significant improvement in patients' quality of life, even as early as 2 weeks postoperatively[5]. Finally, Chapple et al described significant improvements in the impact on QOL survey and the King's Health Questionnaire within 12 weeks of treatment in idiopathic DO patients in a randomized trial[25]. These significant changes in quality of life are important factors to consider, especially with neurogenic patients who are often managing multiple medical conditions. Perceived effects of treatments by the patients enhance the therapeutic benefits. This positive feedback is encouraging as we seek to expand the use of incobotulinumtoxinA for OAB and UI.

Well established side effects after intradetrusor botulinumtoxin A injections include urinary retention, urinary tract infection, dysuria, and bacteriuria. Less frequent side effects include hematuria and pyrexia.

In the first 12 weeks following treatment, Ginsberg et al described UTI incidence of 28% in both treatment groups (200u and 300u), with hematuria and pyrexia occurring in 5% or less in both treatment groups[6]. Nitti et al also described adverse events in the first 12 weeks following injection, showing an incidence of 15.5%[5]. No patients reported adverse effects in this study. This may partly be due to small sample size and short duration of follow-up in this study. However, it is also our practice to treat bacteriuria prior to intradetrusor injection of incobotulinumtoxinA, which may limit the incidence of symptomatic UTI. Overall, the procedure was well tolerated.

One limitation in this study includes the fact that it was a retrospective study. This pilot study has a small sample size and would need to be powered appropriately on a larger scale to draw firmer conclusions. The study population was limited to men because of the site location (VAMC) so generalizability to women should be further explored in larger studies. Future larger placebo-controlled longer-term studies are needed and other populations that should be studied include patients with idiopathic OAB. Other limitations include variations in follow up times between 2-4 weeks. Additionally, no post-injection UDS data was obtained in patients with NDO.

Conclusions

In this preliminary pilot study of a small cohort of males with neurogenic DO and UI, significant improvements were seen following incobotulinumtoxinA injection in daily frequency, number of incontinence episodes, hours in between CIC, and quality of life scores. Larger scale and long-term studies are required to confirm these results, but initial findings are promising for wider use of this formulation.

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Figures and Tables

Fig. 1. Patient Global Impression of Improvement Scores, voiding vs. non-voiding patients.

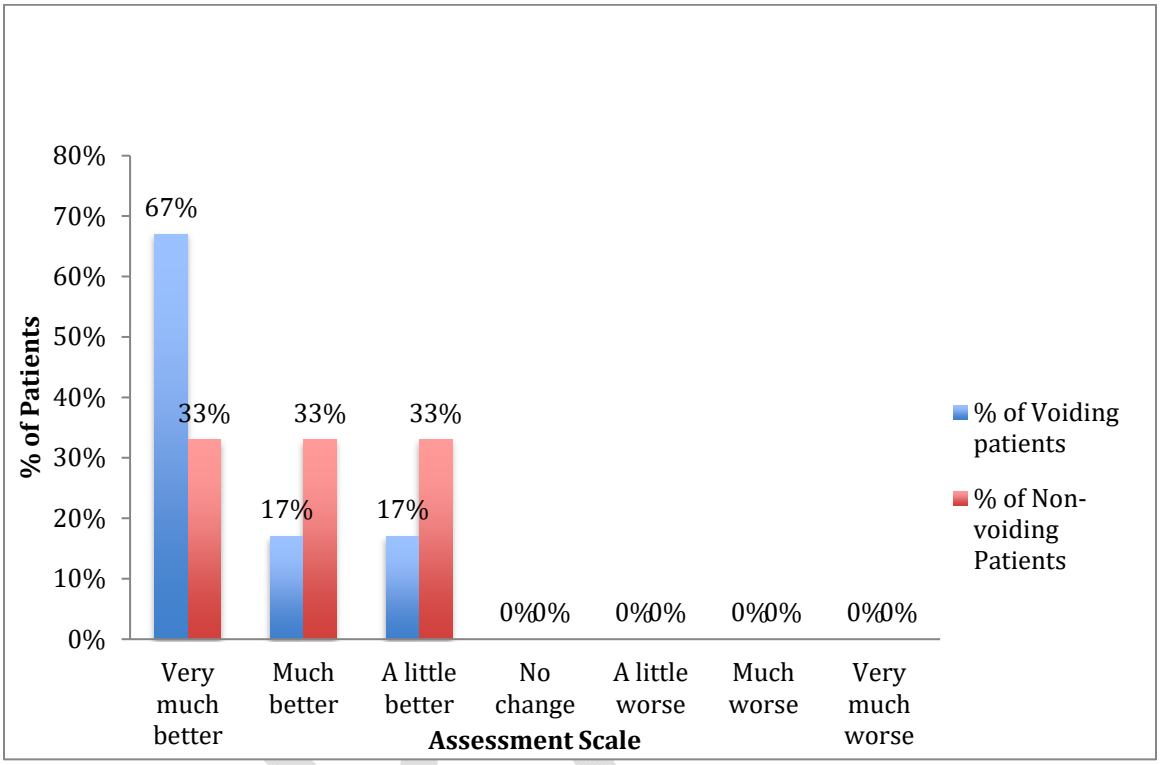

Table 1. Patient demographics	
Total patients	17 (all male)
Age	61.2±15.4 (2181)
Race	**Patients, n (%)**
White	14 (82%)
African American	3 (18%)
Voiding status	**Patients, n (%)**
Voiding	6 (35%)
Chronic in-dwelling tube	6 (35%)
CIC	5 (30%)
Neurological diagnosis	**Patients, n (%)**
SCI	11 (65%)
Cervical SCI	7 (41%)
Thoracic SCI	4 (24%)
MS	1 (6%)
Parkinson's disease	2 (12%)
Stroke	4 (24%)

TBI	5 (29%)
Bladder capacity (mL)	median 215, IQR 200–462.5
Baseline creatinine (mg/dL)	median 0.8, IQR 0.6–1.2
Charlson age comorbidity index	4.3 ± 2.3 (median 4, IQR 2–6.5)
Incobotulinumtoxin A injection history	**Patients, n (%)**
Prior onobotulinumtoxin or incobotulinumtoxin injections before study period	8 (47%)

CIC: clean intermittent catheterization; IQR: interquartile range; MS: multiple sclerosis; SCI: spinal cord injury; TBI: traumatic brain injury.

Table 2. Outcomes following incobotulinumtoxin A injection in CIC patients

	Pre-incobotulinumtoxinA Median (IQR)	**Post-incobotulinumtoxinA Median (IQR)**
Daily pads	0 (0–6)	0 (0–0)
# incontinent episodes daily	2 (1–3)	0 (0–0.25)
Creatinine (mg/dL)	0.7 (0.6–0.8)	0.5 (0.4–0.75)
CIC volumes (mL)	400 (300–500)	550 (400–700)
Hours in between CIC	4 (3–4)	6 (4–6)
UDI6 scores (mean ± SD)	31.5±27.4	8.9±11.5
IIQ7 scores (mean ± AD)	64.3±33.3	9.5±11.2
Patients requiring pads, n (%)	3 (60%)	0 (0%)
Dry patients, n (%)	0 (0%)	5 (0%)

CIC: clean intermittent catheterization; IQR: interquartile range; SD: standard deviation.

Table 3. Outcomes following incobotulinumtoxinA injection in voiding patients		
	Pre-incobotulinumtoxinA Median (IQR)	**Post-incobotulinumtoxinA Median (IQR)**
Daily pads	7.5 (0.75–16.5)	12 (0–18)
Daily frequency	11 (8.5–18)	4 (2–10)
# incontinent episodes daily	2.5 (1–5.5)	1 (0–2)
Creatinine	1.75 (1.2–1.9)	1.7 (1.1–1.9)
UDI-6 scores (mean ± SD)	36.1±43.1	35.1±56.2
IIQ7 scores (mean ± SD)	52.4±40.4	33.3±57.7
Patients requiring pads, n (%)	3 (50%)	2 (33%)
Dry patients, n (%)	0 (0%)	2 (33%)

CIC: clean intermittent catheterization; IQR: interquartile range; SD: standard deviation.

Table 4. Pre and post-incobotulinumtoxinA injection outcomes in patients with chronic indwelling tube (Foley catheters and suprapubic catheters)		
	Pre-incobotulinumtoxinA Median (IQR)	**Post-incobotulinumtoxinA Median (IQR)**
Creatinine mg/dL	0.9 (0.5–1.1)	0.9 (0.6–1)
IIQ7 mean scores (mean ± SD)	39.3±27.8	1.6±2.8
UDI-6 mean scores (mean ± SD)	25±27.4	8.4±11.8
Patients requiring pads, n (%)	1 (17%)	1 (17%)
Dry patients, n (%)	0 (0%)	2 (33%)

CIC: clean intermittent catheterization; IQR: interquartile range; SD: standard deviation.