Management of refractory idiopathic overactive bladder: intradetrusor injection of botulinum toxin type A versus posterior tibial nerve stimulation

Hammouda Sherif, MD, Mostafa Khalil, MD, Rabea Omar, MD
Department of Urology, Faculty of Medicine, Benha University, Egypt

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Introduction: *To compare the safety and efficacy of posterior tibial nerve stimulation (PTNS) versus an intradetrusor injection of botulinum toxin type-A (BTX-A) 100 U in the management of refractory idiopathic overactive bladder (OAB).*

Materials and methods: *We randomized 60 patients with refractory idiopathic OAB to receive an intradetrusor injection of BTX-A 100 U or PTNS. We assessed the patients at baseline, 6 weeks, 3 months, 6 months, and 9 months, and determined their clinical symptoms, overall OAB symptom score, urgency score, quality-of-life score, and urodynamic study parameters.*

Results: *The two patient groups had similar baseline characteristics. After treatment, the patients in the BTX-A group had significant improvements in all parameters compared to their baseline values. Patients in the PTNS group initially had significant improvements in all parameters, but by 9 months, this was no longer true for most parameters. In general, the improvements were more significant in the BTX group, especially at 9 months. In the BTX-A group, two patients (6.6%) needed clean intermittent catheterization; 3 patients (2 women and 1 man; 10% of patients) had mild hematuria, and 2 patients (6.6%) had urinary tract infections (UTIs). In the PTNS group, local adverse effects included minor bleeding spots and temporary pain.*

Conclusions: *Intradetrusor injection of BTX-A and PTNS are both effective to manage refractory idiopathic OAB. BTX-A is more effective than PTNS and is also durable, minimally invasive, reversible, and safe, but it also has more side effects.*

Key Words: overactive bladder, botulinum toxin, posterior tibial nerve stimulation

Introduction

Overactive bladder (OAB) is defined as frequency, nocturia, and urgency (with or without urinary incontinence) in the absence of a urinary tract infection (UTI).[1] Idiopathic OAB is highly prevalent and can be difficult to treat.[2] Many therapeutic options are available to control symptoms, but if OAB is refractory to these therapies, it is important for clinicians to be aware of other treatment options.[3] Initial patient management consists of giving an anticholinergic medication for at least 3 months. If symptoms fail to improve or if the patient is intolerant to medications, other treatment options include neuromodulation and intradetrusor injections of botulinum toxin type A (BTX-A).[4] BTX-A was introduced in Germany in 1998 as a minimally invasive procedure, and it is now an accepted treatment worldwide.[5] BTX-A was approved to treat adults with overactive bladder by the European Union in 2011 and by the US Food and Drug Administration (FDA) in January 2013.[6] The mechanism of action of BTX-A in the urinary bladder has been extensively described.[3,7] In placebo-controlled randomized clinical trials, BTX-A resulted in a significant improvement of symptoms in 50% to 68% of women with idiopathic refractory OAB at 3-6 months.[8,9]

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Address correspondence to Dr. Mostafa Khall, Department of Urology, Faculty of Medicine, Benha University, Egypt

Inhibition of detrusor activity by posterior tibial nerve stimulation (PTNS) was first described by McGuire et al[10] and in 2000 it was approved by the FDA for the treatment of refractory OAB.[11] The posterior tibial nerve arises from spinal roots L4-S3, and these roots carry sensory and motor fibers that innervate the bladder and pelvic floor as well as the urinary sphincter.[12] PTNS is a peripheral nerve stimulation method that involves inserting a needle electrode proximal to the medial malleolus near the posterior tibial nerve. The exact mechanism of action of PTNS is unknown, but it may involve modulation of the nervous system or blood flow.[13,14] There is limited evidence directly comparing the efficacy of PTNS versus BTX-A to treat idiopathic OAB. This study aimed to compare these two treatments for patients with refractory idiopathic OAB.

Materials and methods

Objectives

This was a prospective randomized study to compare the safety and efficacy of an intradetrusor injection of BTX-A 100 U versus PTNS for patients with refractory idiopathic OAB.

Study design

We enrolled 60 patients with idiopathic OAB who presented to the Urology Department at Benha University Hospital from May 2013 to November 2015. The patients had idiopathic OAB symptoms and were 18 years old or older and had not responded to or were intolerant to 3 months of medical therapy with different antimuscarinic agents (alone or in combination). Patients were excluded from the study if they had nerve damage that might affect the function of the posterior tibial nerve or the pelvic floor, or if they were pregnant or planning to become pregnant, or if they had a pacemaker, an implantable defibrillator, current UTI, uncorrectable coagulopathies, or a bladder outlet obstruction, a neurogenic bladder, or a post void residual urine volume > 150 mL. They were also excluded if they had previous radiotherapy or antineoplastic treatment, incontinence surgery, or bladder malignancy, or if they were taking a medication (eg, an aminoglycoside) that might interfere with transmission at the neuromuscular junction, or if they had mixed incontinence. The patients signed an informed consent form and the study was approved by the Research Ethics Committee, Faculty of Medicine, Benha University. Additional use of anticholinergics was not allowed during the study period. Patients were randomized to receive intradetrusor injections of BTX-A 100 U or to undergo PTNS.

Assessment

At baseline, we obtained a patient history and patients had a physical examination, laboratory tests (including a urinalysis and urine culture and sensitivity test), an x-ray of the kidneys, ureters, and bladder, and a pelvic abdominal ultrasound. The patients filled in a bladder-voiding diary for 3 days, which provided information about urinary frequency, urgency, nocturia, and urinary incontinence. The patients also replied to a questionnaire that provided an OAB symptoms score, which has been validated by Blaivas et al.[15] The questionnaire includes 7 questions, for a total score of 0 to 28. Questions 3 to 6 were used to determine an urgency score (from 0 to16), and question 7 was used to determine a quality-of-life score (from 0 to 4). These assessments were repeated at 6 weeks, 3 months, 6 months, and 9 months. The patients had urodynamic parameters determined at baseline and 3 months and 9 months.

BTX-A injection technique

BTX-A (Allergan, Irvine, CA, USA) was prepared by dissolving 100 U into 10 mL of saline. Injection was performed by cystoscopy using a 30-degree lens, in 20 sites (0.5 mL at each site), with a 6 Fr disposable injection needle (Amecath Company, Egypt) under spinal anesthesia. The bladder injection sites at the anterior, left lateral, right lateral, posterior walls, and the trigon were determined after mapping the bladder. At the end of the procedure, a catheter was inserted in the bladder for 24 h. The procedure was carried out under antibiotic prophylaxis (ciprofloxacin 500 mg tablet twice daily for 5 days). If the post-void residual urine volume was greater than 200 mL at any follow up visit, the patient was instructed to perform clean intermittent self-catheterization.

PTNS technique

PTNS was given as a 30-minute session, once a week for 12 consecutive weeks. The nerve was stimulated using a 0.22 mm needle electrode inserted approximately 5 cm cephalic to the medial malleolus and slightly posterior to the tibia. The needle was connected to the Urgent PC stimulator, and the current was increased from 0.5 mA to 9 mA until the patient reported sensation or experienced a muscle response. The frequency was 20 Hz. The response that was sought was a plantar flexion of the great toe.[16]

Statistical analyses

Categorical data were expressed as number and percent, and quantitative data were expressed as mean ± standard deviation. SPSS version 20 software was

TABLE 1. **Patient characteristics**

Variable	BTX group	PTNS group	p value
Mean age (years)	45.6 ± 7.8	45.1 ± 10.1	0.524
Sex			0.718
Male: no. (%)	5 (16.7)	4 (13.3)	
Female: no. (%)	25 (83.3)	26 (86.7)	
Body mass index	36.8 ± 4.9	36 ± 6.2	0.583
Mean duration of treatment by anticholinergics (weeks)	13.3 ± 0.9	13.06 ± 0.8	0.397

BTX = botulinum toxin; PTNS = posterior tibial nerve stimulation

used for the statistical analyses and between-group comparisons were made using the chi-square test, the Fisher exact test, and the student t test. P values were considered significant if < 0.05.

Results

The 30 patients in the BTX-A group and the 30 patients in the PTNS group had similar baseline characteristics, as shown in Table 1.

Within - group analysis

Compared to their baseline values, patients in the BTX-A group had significant improvements in OAB symptom score, urgency score, and quality-of-life score, as shown in Table 2, and they also had significant improvements in their clinical symptoms, as shown in Table 3. They also had significant improvements in urodynamic study parameters at 3 months and 9 months, as shown in Table 4.

Patients in the PTNS group had significant improvements in OAB symptom score and urgency score at 6 months comparted to baseline, but the improvements were not significant at 9 months. However, they had a significant improvement in quality-of-life that persisted until 9 months.

TABLE 2. **Changes in overall OABSS, urgency scale and QoL**

Variable	No.	BTX group	No.	PTNS group	p value
OABSS					
Base line	30	21.7 ± 3.03	30	21.5 ± 2.5	0.748
At 6 weeks	30	13.5 ± 2.8*	30	15.4 ± 2.7*	0.011Δ
At 3 months	30	14.4 ± 2.4*	30	14.7 ± 1.9*	0.666
At 6 months	30	17.6 ± 1.8*	29	18.4 ± 1.9*	0.108
At 9 months	29	19.2 ± 2.4*	28	20.4 ± 1.7	0.026Δ
Urgency scale					
Base line	30	12.6 ± 1.06	30	12.5 ± 1.3	0.833
At 6 weeks	30	7.7 ± 1.7*	30	8.7 ± 1.6*	0.029Δ
At 3 months	30	8.2 ± 1.5*	30	8.6 ± 1.5*	0.356
At 6 months	30	10.1 ± 1.07*	29	10.6 ± 0.8*	0.037
At 9 months	29	10.9 ± 1.3*	28	11.8 ± 1.4	0.009Δ
Quality-of-life					
Base line	30	3.1 ± 0.7	30	3.06 ± 0.8	0.742
At 6 weeks	30	1.9 ± 0.7*	30	2.2 ± 0.6*	0.033Δ
At 3 months	30	2.06 ± 0.6*	30	2.1 ± 0.6*	0.550
At 6 months	30	2.5 ± 0.7*	29	2.6 ± 0.7*	0.477
At 9 months	29	2.6 ± 0.6*	28	2.9 ± 0.6*	0.049Δ

*significant difference to the base line; Δsignificant difference between groups
BTX = botulinum toxin; PTNS = posterior tibial nerve stimulation; OABSS = overactive bladder symptom score

TABLE 3. **Changes in clinical symptoms**

	No	BTX group	No	PTNS group	p value
Frequency					
Base line	30	12.7 ± 0.9	30	12.2 ± 1.2	0.105
At 6 weeks	30	5.7 ± 1.1*	30	6.1 ± 0.9*	0.150
At 3 months	30	6.4 ± 1.04*	30	6.9 ± 0.8*	0.060
At 6 months	30	8.1 ± 1.2*	29	8.9 ± 1.6*	0.036Δ
At 9 months	29	10.7 ± 1.01*	28	11.6 ± 1.09	0.002Δ
Nocturia					
Base line	30	5.2 ± 0.9	30	4.8 ± 0.9	0.143
At 6 weeks	30	1.8 ± 0.7*	30	2.2 ± 0.7*	0.064
At 3 months	30	2.5 ± 0.6*	30	2.8 ± 0.7*	0.063
At 6 months	30	3.1 ± 0.7*	29	4.4 v 0.8*	0.102
At 9 months	29	3.8 ± 1.09*	28	4.4 ± 0.8	0.024Δ
Leaking episodes					
Base line	30	4.3 ± 1.06	30	4.7 ± 1.02	0.178
At 6 weeks	30	1.8 ± 0.7*	30	2.2 ± 0.7*	0.040Δ
At 3 months	30	2.4 ± 0.7*	30	2.6 ± 0.7*	0.287
At 6 months	30	3.06 ± 0.5*	29	3.3 ± 0.6*	0.112
At 9 months	29	3.5 ± 1.2*	28	4.2 ± 1.04	0.020Δ
PVR urine (mL)					
Base line	30	30.6 ± 3.6	30	31.7 ± 3.7	0.225
At 6 weeks	30	45.06 ± 3.7*	30	34.5 ± 3.8*	0.0001Δ
At 3 months	30	42.4 ± 2.04*	30	33.9 ± 2.3*	0.0001Δ
At 6 months	30	39.1 ± 2.4*	29	33.1 ± 2.6	0.0001Δ
At 9 months	29	36.8 ± 2.7*	28	32.4 ± 3.04	0.0001Δ

*significant difference to the base line; Δsignificant difference between groups
BTX = botulinum toxin; PTNS = posterior tibial nerve stimulation; PVR = post void residual

Compared to baseline, the improvements in frequency, urgency, and leaking episodes were significant up to 6 months and the improvement in post-void residual urine volume was significant up to 3 months. There were significant improvements for urine volume at strong desire, and intravesical pressure at 3 and 9 months; whereas the improvement in urine volume at first desire, maximum cystometric capacity, and maximum uroflowmetry was only significant at 3 months.

Between - group analysis

Compared to the PTNS group, patients in the BTX-A group had a significantly greater improvement in frequency at 6 months and 9 months. They also had a greater improvement in nocturia and leaking episodes, with significant differences in nocturia at 9 months and in leaking episodes at 6 weeks and 6 months. The post-void residual urine volume was significantly larger in the BTX group at all follow up times, as shown in Table 3.

The improvement in OAB symptom score, urgency score, and quality-of-life score was greater in the BTX group than in PTNS group, and this difference was significant at 6 weeks and 9 months, as shown in Table 2.

The improvements in the urodynamic study parameters were all significantly greater in the BTX group at 3 months and 9 months, except for urine volume at strong desire, which was not significantly greater at at 3 months.

The study is summarized in the flow diagram, shown in Figure 1.

Adverse events

There were significant differences in the mean post-void residual urine volume after BTX-A throughout the study, but clean intermittent catheterization was only needed only in 2 patients (6.6%) who had a post-void residual urine volume > 200 mL. Early postoperative mild hematuria was observed in 3

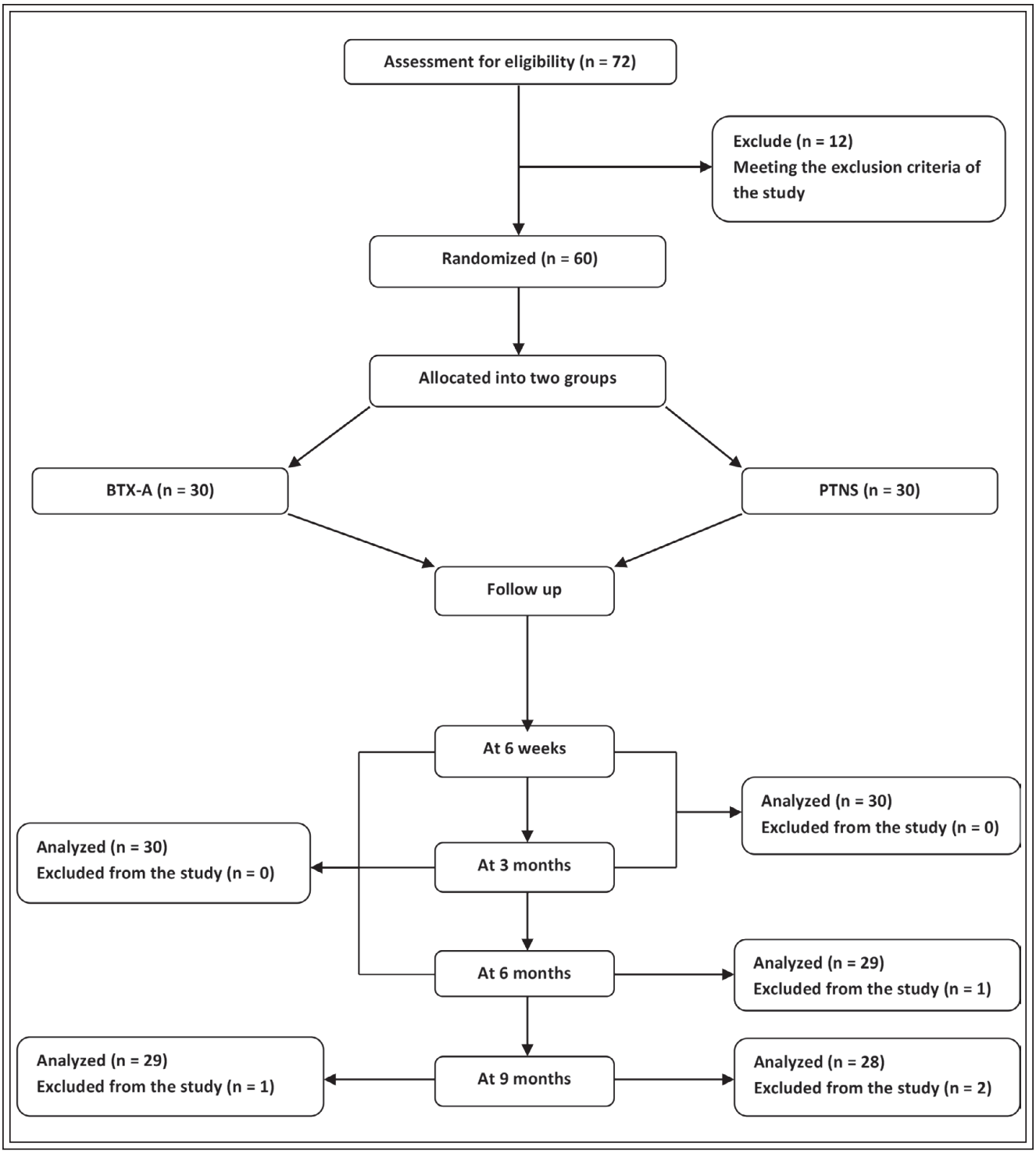

Figure 1. Patient flow diagram.

patients (2 women and 1 man; 10% of patients) after BTX-A. UTI occurred in 2 patients (6.6%). In the PTNS group, local adverse events included minor bleeding spots and a temporary painful sensation.

Discussion

Refractory OAB is a complex, chronic medical problem with deleterious effects on the physical,

TABLE 4. **Urodynamic changes**

Variable	No	BTX group	No	PTNS group	p value
Urine volume at first desire (mL)					
Base line	30	164.2 ± 10.7	30	168.03 ± 7.7	0.119
At 3 months	30	280.8 ± 12.5*	30	274.7 ± 13.1*	0.068Δ
At 9 months	29	177.8 ± 9.2*	28	171.8 ± 7.7	0.008Δ
Urine volume at strong desire (mL)					
Base line	30	248.1 ± 19.9	30	254.5 ± 18.2	0.205
At 3 months	30	383.3 ± 8.5*	30	379.3 ± 7.8*	0.064
At 9 months	29	307.2 ± 16.3*	28	296.8 ± 14.8*	0.012Δ
Intravesical pressure (cm H_2O)					
Base line	30	32.2 ± 1.4	30	31.7 ± 1.6	0.166
At 3 months	30	11.2 ± 0.8*	30	12.1 ± 1.07*	0.001Δ
At 9 months	29	20.7 ± 1.3*	28	21.9 ± 1.4*	0.001Δ
Maximum cystometric capacity (mL)					
Base line	30	277.3 v± 14.3	30	283.6 ± 12.3	0.071
At 3 months	30	423 ± 19.3*	30	406.3 ± 22.1*	0.003Δ
At 9 months	29	304.6 ± 17.6*	28	290 ± 13.1	0.001Δ
Qmax (mL/sec)					
Base line	30	23.1 ± 2.5	30	22.7 ± 2.3	0.523
At 3 months	30	19.4 ± 1.5*	30	20.2 ± 1.3*	0.042Δ
At 9 months	29	20.7 ± 1.6*	28	22.2 ± 1.2	0.001Δ

*significant difference to the base line; Δsignificant difference between groups
BTX = botulinum toxin; PTNS = posterior tibial nerve stimulation

psychological, social, financial, and sexual aspects of life.[17] Traditional effective treatments include behavioral therapy, pharmacotherapy, PTNS, sacral neuromodulation, intradetrusor injection of BTX-A, and bladder augmentation.[18] Patients should select the best treatment that fits their needs.[7] PTNS[4] and intradetrusor injection of BTX-A 100 U[4,19] have been recommended as a third-line therapy for patients who have OAB.

However, to our knowledge, this is the first prospective, randomized study comparing the safety and efficacy of intradetrusor injection of BTX-A 100 U versus PTNS in the management of refractory idiopathic overactive bladder.

We found a significant improvement from baseline in overall OAB symptom score, urgency score, quality-of-life score, and clinical and urodynamic parameters in the BTX-A group, up to 9 months after the injection. Other studies have reported significant reductions in frequency and incontinence episodes[20,21] and urgency following BTX-A treatment in patients with OAB.[20,22,23] Symptoms improved up to 6 months and then began to decay, although at 12 months, the symptom levels had not yet returned to baseline.[24]

In the current study, with PTNS, comparted to baseline values, there was a significant improvement in OAB symptom score, urgency score, frequency, nocturia, and leaking episodes at 6 weeks, 3 months and 6 months. There are many different PTNS protocols (with different numbers of sessions and different session duration), and no studies have been performed to identify the best modalities. Success rates for PTNS range from 37% to 93%.[11,25] Some studies have reported PTNS is efficacy for treating urinary frequency, urgency urinary incontinence,[11,34] and improving post-void residual urine volumes volumes[26] but limited efficacy for treating nocturia and urgency.[27] Other studies have reported improvements in voiding parameters and quality-of-life outcomes after 5 to 12 weeks of treatment.[28-30] Many authors have established that PTNS significantly improves OAB symptoms. The primary weakness identified by this group of publications is the lack of long term follow up in a randomized design.[11,25,27,31,32]

Adequate follow up after initial treatment is needed to assess improvements of symptoms and patient satisfaction with treatment. The current study reported a significant improvement at 6 weeks in OAB

symptom score, urgency score, quality-of-life score and leaking episodes in favor of the BTX-A group. There were no significant between-group differences for other parameters. At 3 months, results in the two groups were comparable for OAB symptom score, urgency score, and quality-of-life score, and the clinical variables were in favor of the BTX-A group. At 6 months, there was a significant difference in frequency and post-void residual urine volume in the BTX-A group. All parameters were significantly better in the BTX-A group at 9 months, which suggests that this treatment was more durable than PTNS.

Nuhoglu et al[33] evaluated patients 1 year after 10 weeks of Stoller afferent nerve stimulation (SANS) therapy. Without continuous treatment, complaints of urgency urinary incontinence and frequency returned to pretreatment levels. Macdiarmid et al[16] followed 35 patients with OAB who had completed 12 weekly PTNS sessions and were offered 9 more months of treatment. The benefit from PTNS therapy remained stable. The ability to compare patient-reported outcomes across published studies is limited by a lack of standardization due to the development of many different questionnaires to assess OAB symptoms.[34] Improved scores were reported on King's Health Questionnaire,[35] I-QoL scores,[26] IIQ-7 and UDI-6.[22]

Urodynamics are a part of the physical examination of patients with refractory OAB, which is the gold standard for detrusor overactivity diagnosis.[36] It is important to understand that not every patient with OAB needs urodaynamic studies to determine detrusor overactivity, and it is valuable to use urodynamic studies to evaluate new treatment modalities.[37] In our study, urodynamic parameters were only assessed at baseline and 3 months and 9 months after the initial procedure, due to the invasiveness of these studies. At 3 months, there was a significantly greater improvement in favor of BTX-A for all variables except urine volume at strong desire. At 9 months there was a significant improvement in favor of BTX-A for all parameters.

Various studies have reported improvements in a variety of urodynamic parameters.[22,24] In contrast, Cohen et al reported that no preoperative urodynamic parameter predicted successful treatment with 100-150 U BTX-A for OAB patients.[38] Schmid et al reported that all non-responders showed low pretreatment detrusor compliance and maximum bladder capacity less than 100 mL, which was explained due to bladder wall fibrosis.[39]

In the current study, there were no systemic adverse events in the PTNS group, but that group had local effects in the form of bleeding spots and temporary painful needle insertion. In general, other studies have not reported any serious adverse events with PTNS. The adverse events included generalized swelling, worsening of incontinence, headache, hematuria, leg cramps, vasovagal response to needle placement, minor bleeding or a temporary pain at insertion site and tingling in the leg.[26] On other hand, side effects of BTX-A injection may include gross hematuria, UTI, transient muscle weakness, post-void residual urine volume, and urinary retention.[22,35] In our study, there was a statistical difference in the mean post-void residual urine volume after BTX-A throughout the study but clean intermittent catheterization was only needed for two patients (6.6%) who had a post-void residual urine volume > 200 mL. Urine retention was not reported in this study. In other studies of BTX-A for OAB, large post-void residual volume has been defined as > 150 mL to > 350 mL, and has been reported to range from 0% to 75%,[20,40] and the reported need for clean intermittent self catheterization ranges from 0% to 48%.[20,41]

Reported rates (4%-43%) of urinary retention are the main drawback with BTX-A.[4,42] A large post-void residual volume, and urine retention remain obstacles for BTX-A use, and no factors that predict these adverse effects have been found.[43] Bauer et al[44] concluded that higher doses of the toxin led to higher adverse event rates. In our study, early postoperative mild hematuria was observed in 3 patients (2 women and 1 man; 10% of patients) after BTX-A, which was related to the procedure and was resolved with conservative treatment, which is similar to what has been reported in the literature.[8,45]

The other side effect in our study was UTI, which occurred in 2 patients (6.6%) despite prophylactic antibiotic use. These cases were undergoing clean intermittent catheterization and received appropriate antibiotics based on urine culture and sensitivity test results. This agrees with the reported UTI rates in patients with OAB in the literature.[26,39]

The major limitations of this study were the lack of a randomized control group, the limited number of patients, and the lack of cost data. PTNS requires repeat sessions, possibly for a long time or lifelong. There is a lack of standardization of OAB symptoms due to the development of numerous OAB questionnaires. To our knowledge, there has not been a cost-benefit analysis for these treatments. At our university hospital, the cost is covered by the government, but clearly consultation every week for 12 weeks for PTNS is different from a BTX-A injection every 9 to 12 months, although the costs may be very different.

Nowadays, magnetic PTNS can stimulate the nerve without needles, at home. A device marketed by EM

Kinetics (Mission Viejo, CA, USA) called the Transtim was reported to achieve improvement in overall bladder symptoms.[46] Chuang used liposome encapsulated BTX-A as a new approach to reduce its invasiveness.[47]

Conclusions

Intradetrusor BTX-A injections and PTNS are both effective treatments for refractory idiopathic OAB. BTX-A is more effective than PTNS, and is durable, minimally invasive, reversible and safe, but it has more side effects. The optimum number and duration of PTNS sessions remain to be determined. □

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