The Clinical and Urodynamic Results of Percutaneous Posterior Tibial Nerve Stimulation on Neurogenic Detrusor Overactivity in Patients With Parkinson's Disease

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OBJECTIVE To investigate the effect of percutaneous posterior tibial nerve stimulation (PTNS) treatment after 12 weeks on urodynamic and clinical findings in patients with Parkinson's disease (PD) with neurogenic detrusor overactivity.

METHODS A total of 47 patients with PD with neurogenic detrusor overactivity were enrolled in the study. Urodynamic studies before and after 12-week PTNS treatment were performed. International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), Overactive Bladder Questionnaire (OAB-V8), and Overactive Bladder Questionnaire Short Form (OAB-q SF) have been assessed before and after PTNS treatment.

RESULTS The mean first involuntary detrusor contraction volume (*1st* IDCV) on standard cystometry was 133.2 ± 48.1 (24-265) mL, whereas it was 237.3 ± 43.1 (145-390) mL after PTNS. The mean maximum cystometric capacity (MCC) on standard cystometry was 202.2 ± 36.5 (115-320) mL, whereas it was 292.1 ± 50.6 (195-395) mL after stimulation. The improvements in the first involuntary detrusor contraction volume and maximum cystometric capacity were statistically significant after stimulation. The mean Pdetmax at first involuntary detrusor contraction, maximal detrusor pressure at maximum cystometric capacity, PdetQmax, Qmax, and post-void residual volume were statistically significant after 12-week stimulation. Mean parametric improvements at 12-week PTNS treatment from baseline included daytime frequency decreased by 5.6 voids daily, urge incontinence decreased by 3.1 episodes daily, urgency episodes decreased by 6.3 episodes daily, nocturia decreased by 2.7 voids, and voided volume improved by a mean of 92.6 mL. The change from baseline on the ICIQ-SF, OABv8, and OAB-q at 12-week PTNS treatment demonstrated statistically significant improvements.

CONCLUSION These results have demonstrated that PTNS improves the lower urinary tract symptoms and urodynamic parameters in patients with PD. UROLOGY 87: 76–81, 2016. © 2015 Elsevier Inc.

Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by loss of dopaminergic neurons and is characterized by both motor and non-motor problems. The non-motor problems of PD are neuropsychiatric disorders, sleep disorders, sensory symptoms, and autonomic disorders.[1] Lower urinary tract symptoms (LUTS) including urgency, increased daytime frequency, nocturia, and urge urinary incontinence are the most common autonomic disorder in patients with PD.[1,2] Urodynamic abnormalities, including neurogenic detrusor overactivity (NDO), hyporeflexia or areflexia, decreased capacity, and abnormalities of external sphincter function, have been commonly reported in patients with PD.[3] LUTS frequency was estimated as 30% at onset, whereas it was estimated as 70% after 5 years. LUTS in PD have not been shown as a significant threatening cause of upper urinary tract involvement because patients with PD suffer from NDO bladder without detrusor sphincter dysynergia.[4,5] LUTS lead to decreased quality of life (QoL) for patients with PD.[1,4,6] The current management of LUTS involves not only palliation of neurological and motor deterioration but also improvement of NDO symptoms sig-

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nificantly affecting the QoL of patients.[6] Different managements, including the use of pharmacotherapy and surgery, have been proposed, but they usually do not restore functional synergy. If patients are refractory to pharmacologic treatment of NDO or cannot tolerate the side effects, repeated intramuscular injections of botulinum toxin (BTX) into the detrusor could be considered.[6] Several sites have been widely used to treat urinary disorders for neuromodulation including the sacral, pudendal, tibial, and genital nerves, but the most widely reported area for the treatment of overactive bladder (OAB) has been the third sacral nerve root (S3).[7] Percutaneous posterior tibial nerve stimulation (PTNS) is a minimally invasive neuromodulation technique that has been shown to be an effective treatment for patients with neurogenic and nonneurogenic LUTS unresponsive to medical treatment.[8] The efficacy of 12-week PTNS treatment to improve idiopathic OAB symptoms has been established through randomized, controlled trials, with long-term durability, and sustained therapeutic effects during 12 and 24 months.[8-11] Moreover, few studies have been performed to determine the effects of PTNS on NDO in patients, especially, with PD. In our previous studies, we reported the effects of PTNS with acute urodynamic parameters on NDO in patients with PD. Also, we found an increase of first involuntary detrusor contraction volume (*1st* IDCV) and of maximum cystometric capacity (MCC) in patients with NDO.[12] However, to our knowledge, no current study has been reported to evaluate the urodynamic and clinical effects of chronic PTNS treatment of PD patients with NDO.

The aim of this study was to determine the effects of PTNS treatment which was applied once a week for a period of 12 weeks on the urodynamic and clinical findings in PD patients with NDO.

MATERIALS AND METHODS

This study was approved by the local ethic committee. All patients were informed for the details of all procedures and for the details of the study. Written informed consent was obtained from all participants according to their own will. All patients with PD who were treated in our hospital were screened. The patients with PD which included in the study that had LUTS were selected from our neurology clinic. All patients diagnosed with PD or Parkinsonism were extracted on the basis of the medical records. Then, only the patients who fulfilled the following inclusion criteria were selected. The patients who participate in the study received the urinary sediment test for screening urinary tract infection before the start of the study as well as on every visit to the hospital throughout the study period. The core symptoms of PD were monitored by Unified Parkinson's Disease Rating Scale (UPDRS) part 3 total score to study the relationship of Parkinsonian symptoms. Patients with PD, who had storage symptoms such as urgency, increased daytime frequency, nocturia, and urge urinary incontinence, were included in the study. All patients with PD with urinary complaints completed the questionnaires for International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), Overactive Bladder Questionnaire (OAB-V8), and Overactive Bladder Questionnaire Short Form (OAB-q SF) before and after PTNS. The inclusion criteria for PD patients with neurogenic bladder symptoms were self-reported bladder symptoms ≥3 months, self-reported failed conservative care, and those who discontinued all antimuscarinics for ≥2 weeks. Also the patients who were capable of giving informed consent, ambulatory, and able to use toilet independently without difficulty were included. The exclusion criteria were sacral peripheral nerve lesions, urinary tract infection, marked prostatic enlargement on digital rectal examination, bladder stones, age younger than 18 years, diabetes mellitus and severe cardiopulmonary disease, and stress urinary incontinence. Also the patients who were not willing to continue the study or who had BTX treatment for neurogenic bladder within the past 1 year, and those who had pacemakers or implantable defibrillators were excluded. Patients with history of previous continence surgery, current bladder malignancy, high-grade dysplasia, or carcinoma were also excluded from the study. The patients were requested to complete a 3-day voiding diary before and after the treatment of PTNS. Clinical success was considered to be a complete response as 100% reduction for urgency episode, urinary incontinence episode, daytime frequency episode, and nocturia compared with the baseline findings. Decreases between 75% and 100%, 50% and 75%, and 25% and 50% were considered to be a good, partial, and poor response, respectively. A decrease <25% was considered as no responders.

Posterior Tibial Nerve Stimulation

PTNS was applied unilaterally with 26-gauge stainless steel needles (disposable concentric needle, Medtronic, Denmark) inserted 5 cm cephalad from the medial malleolus and posterior to the edge of the tibia. Electrical stimulation (Medtronic Key Point Net, Denmark) was applied unilaterally by using charge-compensated 200 μs pulses with a pulse rate of 20 Hz, as used in previous studies.[12,13] The intensity level was then chosen as the intensity immediately under the threshold determining motor contraction. Electrical stimulation was triggered with a push button to determine the appropriate stimulation amplitude and to confirm the correct needle placement. The stimulation amplitude was set at the maximum tolerable level according to the subject under investigation, which was usually 1.5 times the threshold for evoking plantar flexion of the toes or toe fanning (range: 1-5 mA).

Urodynamic Measurements

The urodynamic evaluations were complied with International Continence Society (ICS) recommendations. Cystometry was done with the patient in the supine position (MMS Solar Digital Urodynamy Device, Dover). Intravesical and abdominal pressures were measured with double lumen 8 Fr air-charged catheters with a rectal balloon (T-DOC Company, Wilmington, DE). Cystometry was done with normal saline at room temperature. The filling rate was 50 mL/min. OAB was confirmed in these patients with involuntary detrusor contraction demonstrated during routine cystometry. Any involuntary detrusor contraction that occurred during the filling phase was considered evidence of NDO. First cystometry was performed before PTNS. Volume at the *1st* IDC, maximal detrusor pressure (Pdetmax) at first involuntary detrusor contraction, MCC, maximal detrusor pressure at MCC (Pdetmax), detrusor pressure at maximal flow (PdetQmax), maximal flow rate (Qmax), and post-void residual volume (PRV) were noted. The detrusor pressure was calculated as the difference between the intravesical and abdominal pressures ($P_{ves} - P_{abd}$). Second cystometry was performed after 12-week PTNS treatment. Control urodynamic evaluations were performed for the patients 1 week after 12-week PTNS treatment. MCC was defined

as the volume at which the patient feels he or she can no longer delay micturition in patients with normal sensation (has a strong desire to void). *1st* IDCV is defined as the first detected volume during filling cystometry in first involuntary detrusor contraction. Pressure-flow analysis was performed in all patients, monitoring detrusor pressure and urinary flow. External sphincter electromyography (EMG) was recorded by surface EMG patches at the 3- and 9-o'clock positions to the anus. After all tubes and EMG patches had been placed, the patient then stood up. The definition of BOO was based on the provisional International Continence Society definition of obstruction. BOO was defined when the pressure-flow study showed a PdetQmax greater than 50 cm H_2O or an Abram's-Griffiths number (defined as PdetQmax − 2 × Qmax) greater than 40. Urethral sphincter pseudodyssynergia (bradykinesia) was diagnosed when the pressure-flow study demonstrated high PdetQmax and low Qmax in combination with increased sphincter EMG activity during voiding.

Statistical Analysis

The baseline demographic and clinical features such as age, gender, scores, the duration of the disease of the participants, and UPDRS were evaluated with the analysis of variance test (ANOVA). Mean values of symptoms and urodynamic parameters were evaluated for significant change using a 2-sided paired *t* test and median values were evaluated using a Wilcoxon signed rank test with $P < .05$ considered statistically significant.

RESULTS

A total of 47 patients with a mean age 61 ± 8.3 years (range 44–79) were enrolled in the study. Of these 47 patients, 26 patients (55.3%) were men and 21 patients (44.7%) women. Mean duration PD was 7.3 ± 3.8 years; duration of LUTS was 3.6 ± 2.4 years. UPDRS part 3 score of the study was 16.7 ± 7.6 points, whereas it was 16.3 ± 7.5 after PTNS. The initial and post-treatment UPDRS scores were not different statistically ($P > .05$). Mean *1st* IDCV on standard cystometry was 133.2 ± 48.1 (24-265) mL, whereas it was 237.3 ± 43.1 (145-390) mL after PTNS. Mean MCC on standard cystometry was 202.2 ± 36.5 (115-320) mL, whereas it was 292.1 ± 50.6 (195-395) mL after stimulation. The improvements in the *1st* IDCV and MCC were statistically significant after stimulation when compared with baseline data ($P < .001$ for each). Mean Pdetmax at first involuntary detrusor contraction, maximal detrusor pressure at MCC, PdetQmax, Qmax, and PRV were statistically significant after 12-week stimulation when compared with baseline data ($P < .001$) (Fig. 1, Table 1). When first involuntary detrusor contraction pressure cutoff value was 10 cm H_2O, the detrusor contraction was suppressed in below 10 cm H_2O after PTNS in 26 patients (55.3%). PTNS was effective to completely relieve the findings of pseudodyssynergia in 7 of the 11 (63.6%) patients with pseudodyssynergia. The improvements after 12-week PTNS treatment all voiding diary parameters were statistically significant compared with baseline. Mean parametric improvements at 12-week PTNS treatment from baseline included daytime frequency decreased by 5.6 voids daily ($P < .001$), urge incontinence decreased by 3.1 episodes daily ($P < .001$), urgency episodes decreased by 6.3 episodes daily ($P < .001$), nocturia decreased by 2.7 voids

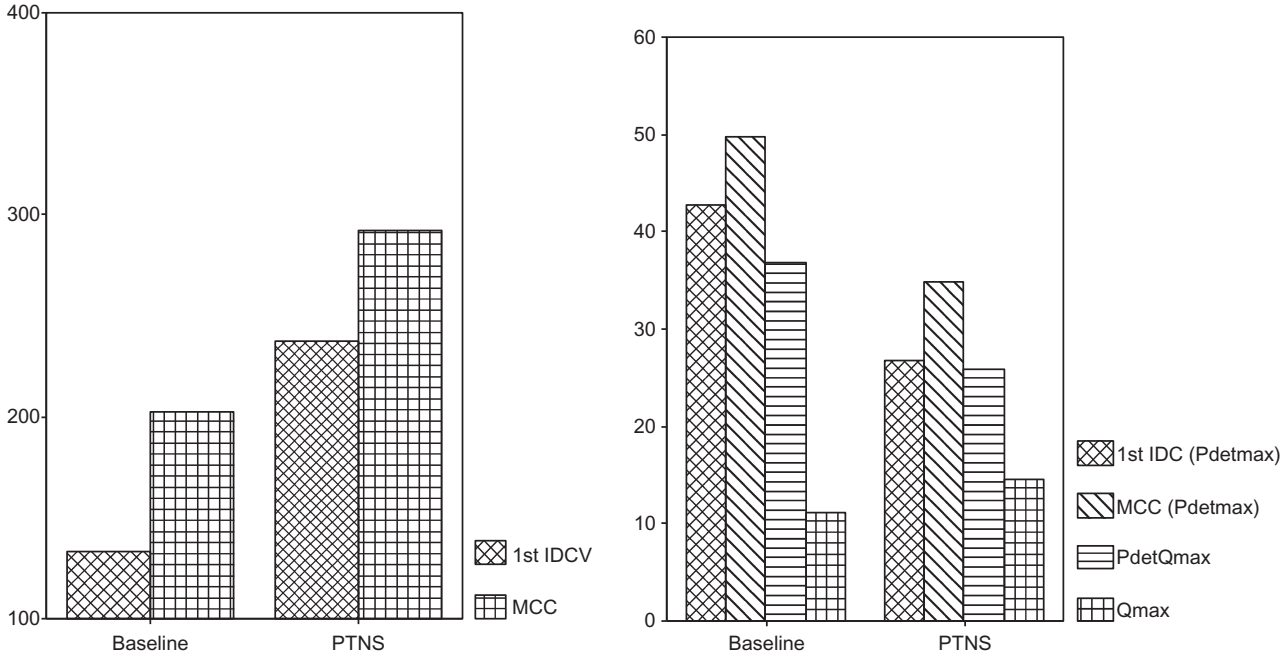

Figure 1. The effects of PTNS on the following urodynamic variables: first involuntary detrusor contraction (*1st* IDCV), volume at maximum cystometric capacity (MCC), maximal detrusor pressure (Pdetmax) at first involuntary detrusor contraction, maximal detrusor pressure at maximum cystometric capacity (Pdetmax), detrusor pressure at maximal flow (PdetQmax), and maximal flow rate (Qmax) for the comparison of baseline and after PTNS treatment.

Table 1. The effects of posterior tibial nerve stimulation (PTNS) on urodynamic variables for the comparison of baseline and after PTNS treatment

Urodynamic Variables	Baseline Value Mean ± SD (Range)	PTNS Mean ± SD	*P* Value
First involuntary detrusor contraction			
At volume (mL)	133.2 ± 48.1 (24-265)	237.3 ± 43.1 (145-390)	.000
Pdetmax (cmH_2O)	42.7 ± 19.6 (12-98)	26.8 ± 10.1 (9-51)	.000
Maximum cytometric capacity			
At volume (mL)	202.2 ± 36.5 (115-320)	292.1 ± 50.6 (195-395)	.000
Pdetmax (cmH_2O)	49.7 ± 21.8 (18-95)	34.7 ± 11.5 (13-66)	.000
PdetQmax	36.8 ± 11.1 (16-67)	25.9 ± 7.5 (9-43)	.000
Qmax (mL/s)	11.2 ± 2.2 (5-16)	14.4 ± 4.8 (6-32)	.000
Post-void residual volume (mL)	73.7 ± 46.3 (0-213)	43.4 ± 22.8 (0-97)	.000

Pdetmax, maximal detrusor pressure; PdetQmax, detrusor pressure at maximum flow rate; Qmax, maximum flow rate; SD, standard deviation.

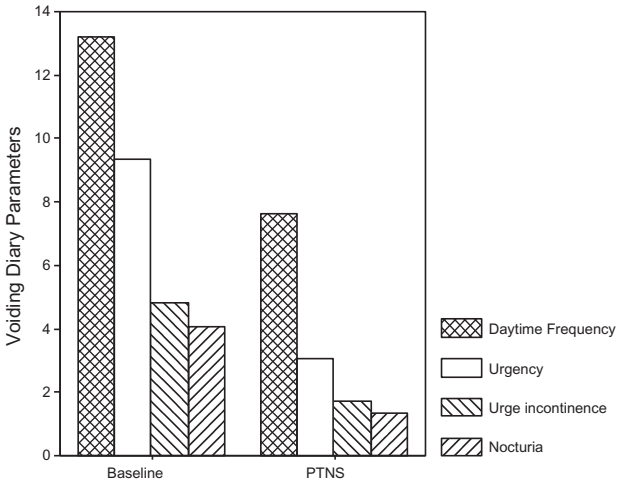

Figure 2. Changes in voiding diary parameters for the comparison of baseline and after PTNS treatment.

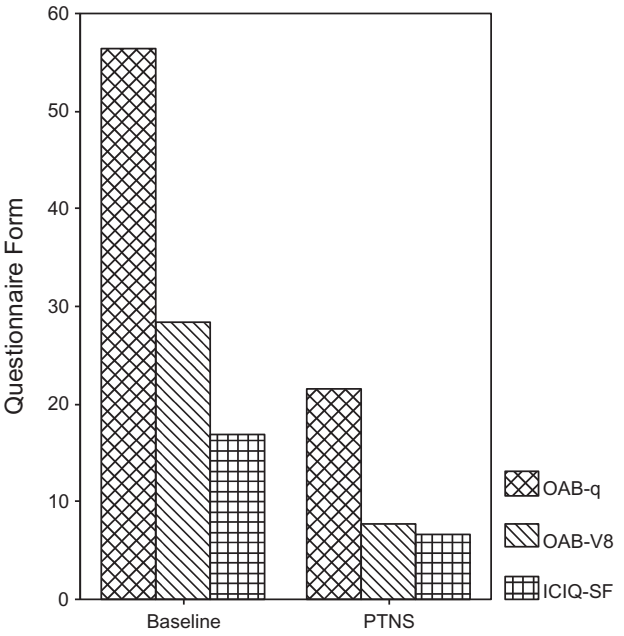

Figure 3. International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), Overactive Bladder Questionnaire (OABv8), and Overactive Bladder Questionnaire Short Form (OAB-q) changes from baseline.

(*P* <.001), and voided volume improved by a mean of 92.6 mL (*P* <.001) (Fig. 2). The change from baseline on the ICIQ-SF, OABv8, and OAB-q at 12-week PTNS treatment demonstrated statistically significant improvements in symptom severity and health-related QoL (*P* <.001) (Fig. 3). A clinical complete response for urgency episode, urinary incontinence episode, daytime frequency episode, and nocturia after 12 weeks of PTNS was observed in 10.6%, 12.8%, 8.6%, and 17% of the patients, respectively; good response was observed in 21.3%, 23.4%, 14.9%, and 19.1% of the patients, respectively; partial response was observed in 21.3%, 19.1%, 19.1%, and 23.4% of patients, respectively; poor response was observed in 31.9%, 25.6%, 36.1%, and 19.2% of patients, respectively (*P* <.001). There were no reported treatment-related adverse events in the patients through 12 weeks. Seven patients reported mild to moderate pain such as in the site of the puncture, leg cramps, and tingling in the leg events with an unknown relationship to the PTNS treatment.

COMMENT

LUTS are common autonomic disorders in PD. It is well understood fact that degeneration of the nigrostriatal dopaminergic pathway occurs in PD. Degeneration of dopaminergic pathway states many of the motor disorders were encountered in patients with PD. The effect of the basal ganglia on voiding is thought to be inhibitory.[1,2] However, the principal cause of LUTS present with PD is poorly understood. In contrast to motor disorders, LUTS is sometimes non-responsive to levodopa treatment.[14] In PD, urodynamic findings of DO correlate well with diagnosis made by questionnaires; and patients with PD do not have visible true detrusor-sphincter dyssynergia as the pontine micturition center is not involved.[5] Treatment of patients with PD due to LUTS should be noted on lowest morbidity and highest QoL by improvement of the symptoms and the ability to get over different resistant to other treatment. Conservative management with behavioral modification and anticholinergic drugs are routinely used

for patients with PD. In some patients, anticholinergic drug treatments may have no efficacy for LUTS. Moreover, these drugs may have side effects, which can result in the interruption of treatment despite its efficacy. Therefore, alternative treatment has been recommended before surgical intervention, such as neuromodulation and BTX injections into the detrusor.[6] The mechanism of PTNS effect in neurogenic bladder is still not well clarified even many studies have been made previously. Danisman et al found that after PTNS, the mast cell count in the bladder of female rats diminished.[15] Chang et al demonstrated that PTNS could produce the effect on the spinal cord by reducing C-fos expression (a marker of neuronal metabolic activity), in rat sacral spinal cord, after electrical stimulation of the hind leg.[16] Finazzi-Agro et al have reported the effect of PTNS on supraspinal centers and found a significant increase in amplitude of long latency somatosensory evoked potentials recorded 24 hours after the end of a 12-session PTNS program. This finding could reflect a modification in elaboration mechanisms of sensory stimuli and it suggests a possible reorganization of cortical excitability after PTNS.[17] Zhang et al suggest that the inhibition of reflex bladder activity by sacral neuromodulation occurs primarily in the central nervous system by inhibiting the ascending or descending pathways of the spinobulbospinal micturition reflex in cats.[18] PTNS was first described by McGuire et al in patients with incontinence, using a transcutaneous electrode over the common peroneal or posterior tibial nerve and a contralaterally placed ground electrode over the same nerve.[19] Later on, Stoller et al adjusted this method by using a percutaneous needle electrode and placing the ground electrode on the ipsilateral extremity.[20] Since then, many studies have been done to evaluate PTNS as a treatment in patients who presented with symptoms of OAB. These studies have demonstrated good results and urodynamic parameters were improved after treatment. A statistically significant decrease was observed in leakage episodes, the number of pads used, voiding frequency and nocturia, and an equal increase in the mean and smallest volumes voided.[7-13] Finazzi-Agro et al have reported the effects of PTNS in 35 women with refractory, idiopathic DO and showed that 71% of patients treated with PTNS had a reduction of urge incontinence episodes greater than 50% (P <.001).[8] A literature review produced by Cone et al reported 92% overall success rate in patients with NDO, as defined by >50% improvement in bladder diary variables.[21] To our knowledge, few studies have been performed to determine the effects of PTNS on NDO in patients with PD. In our previous studies, we reported the effects of PTNS with acute urodynamic parameters on NDO in patients with MS and patients with PD; we also found an increase of first involuntary detrusor contraction volume and of cystometric capacity in patients with NDO.[12,22] Also in another study, we investigated the effect of PTNS in MS patients with NDO and we reported improvements in urodynamic and voiding parameters after 12-week PTNS treatment.[23] Up to the present, any study has been performed to determine the urodynamic and clinical effects after 12 weeks following PTNS on NDO in patients with PD. The 12-week results of our study demonstrated the strong evidence that PTNS has urodynamic and clinical effects for NDO in patients with PD. The voiding diary parameters of daytime frequency, nocturia, urge incontinence episodes, and urgency episodes were all significantly improved from baseline (P <.001, for all parameters). Consistent with the results of objective voiding diary, the ICIQ-SF, OABv8, and OAB-q scores further confirm improvement after 12-week treatment, reflecting the clinical significance of changes for patients.

In a prospective study, Ohannessian et al had showed the significantly increased cystometric capacity (211 mL ± 106 to 260 mL ± 226, P = .6) and subjective improvement of QoL in women with PD or multiple system atrophy and concomitant NDO for evaluation of the efficacy of chronic transcutaneous tibial nerve stimulation (TTNS).[24] In another study, it was reported that TTNS is effective in the treatment of LUTS in patients with PD, which reduces urgency and nocturia episodes and improves urodynamic parameters as well as symptom scores measured by the OAB-V8 and health-related quality-of-life scores measured by the ICIQ-SF.[25]

BTX has been demonstrated in pilot and pivotal trials to be quite effective in reducing idiopathic OAB and NDO symptoms.[26] Anderson et al reported 100 IU injections of BTX as an office procedure for NDO due to PD. Their results showed a moderate improvement in symptoms at 3 months in close to 60% of patients.[27] Giannantoni et al also showed the improvement in frequency and QoL in 4 patients with PD who received 200 U of BTX injections in the bladder.[28]

The outcomes of sacral neuromodulation (SNM) in patients with NDO have not been fully demonstrated. Wallace et al showed that in patients who underwent SNM treatment with LUTS due to multiple sclerosis (MS) and PD, the incontinence episodes, frequency, and nocturia were decreased. There was 93% patient satisfaction.[29] A recent meta-analysis of 26 independent studies (n = 357 patients) showed that SNM is effective and safe for the treatment of NDO; the pooled success rates were 68% for the test phase and 92% for permanent SNM.[30] To our knowledge, there is no study comparing the effects of PTNS with BTX or SNM for NDO. But it is shown that the PTNS may be the potentially beneficial effective therapy for the treatment of NDO. However, we believe that these results should be verified with a prospective multicenter in a study with a larger number of subjects.

CONCLUSION

The findings in this study demonstrated the improvements of LUTS and urodynamic parameters in patients with PD after 12-week PTNS treatment. These results must be confirmed by randomized controlled studies to assess the exact role of PTNS in these indications and to evaluate the long-term durability of the treatment.

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