Outcomes following Percutaneous tibial nerve stimulation (PTNS) treatment for neurogenic and idiopathic overactive bladder

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Abstract

Purpose: Percutaneous Tibial Nerve Stimulation is a minimally invasive neuromodulation technique for treating overactive bladder symptoms. The aim of this study was to assess safety, efficacy and impact on quality of life of Percutaneous Tibial Nerve Stimulation in neurological patients reporting overactive bladder symptoms.

Methods: In this retrospective evaluation over 18 months at a tertiary healthcare center, patients finding first-line treatments for overactive bladder ineffective or intolerable, underwent a standard 12-week course of Percutaneous Tibial Nerve Stimulation (Urgent PC, Uroplasty). Symptoms were evaluated using standardised International consultation on incontinence questionnaires and bladder diaries.

Results: Of 74 patients (52 women, 22 men, mean age 56 years) forty-nine (66.2%) patients had neurological disorder (19 (25.7%) multiple sclerosis and 30 (40.5%) other neurological conditions) and 25 (33.8%) idiopathic overactive bladder. Overall for the entire cohort significant improvements were recorded after 12 weeks in following domains: 24 hour frequency on bladder diary -1.67 (-3.0, 0.33) (p=0.002), number of incontinent episodes on bladder diary -0.0 (-1, 0) (p=0.01), incontinence severity on bladder diary 0 (-0.33, 0) (p=0.007), OAB symptoms -3 (-11.5, 5) (p=0.01), and quality of life -16 (-57, 6.5) (0.004). There were no significant differences in outcomes between patients with idiopathic and neurogenic overactive bladder.

Conclusions: Percutaneous Tibial Nerve Stimulation appears to be a possible promising alternative for patients with neurological disorder reporting overactive bladder symptoms who find first line treatments either ineffective or intolerable. However, a properly designed study is required to address safety and efficacy.

Keywords: percutaneous electric nerve stimulation; overactive bladder; multiple sclerosis; lower urinary tract symptoms; quality of life

Introduction

Percutaneous tibial nerve stimulation (PTNS) is a minimally invasive neuromodulation technique for treating overactive bladder (OAB) symptoms. The tibial nerve is a mixed nerve that contains fibers from spinal roots L4 through S3, that innervates lower urinary tract (LUT) and supply pelvic floor [1]. The insertion point of the needle that lies over the tibial nerve corresponds to Sanyinjiao (SP6) point traditionally used in Chinese acupuncture for a variety of urinary disorders [1]. Largely free of adverse effects, this treatment is potentially attractive for patients finding the first line treatment for OAB, antimuscarinic medications, ineffective or intolerable [2]. Alternative second line treatments such as sacral neuromodulation (SNM) require specialist surgical expertise and the need for revision procedures after three to seven years because of a finite battery life [3]. Botulinum toxin-A is another effective second-line option, however, is associated with the risk for developing urinary retention and therefore the need for catheterisation [4]. Several studies have demonstrated the safety and efficacy of tibial nerve stimulation in patients without a neurological disease reporting OAB symptoms (idiopathic OAB) [5,6] and a 12 weeks course of once-weekly 30-minute PTNS was shown to be superior to sham treatment in a multi-centric, double blind, randomised study, the SUmiT Trial [7]. The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom has issued guidance on the use of PTNS for managing OAB symptoms, and this option has been included in published guidance for the management of urinary incontinence in women [8,9]. On the other hand, studies evaluating PTNS in patients with neurological disorder are few. Kabay et al. studied the benefits of PTNS in a small number of patients with multiple sclerosis (MS) and Parkinson's disease (PD) demonstrating improvements in urodynamic parameters such as maximum cystometric capacity and first involuntary detrusor contraction during bladder filling [10-12]. Another study demonstrated clinical benefit in patients with MS with OAB unresponsive to antimuscarinic medications [13-16].

The mechanism by which PTNS works is unclear, and it is likely that PTNS acts through neuronal pathways, possibly mediated through alterations in cerebral endorphin levels, depolarization of somatic sacral and lumbar afferent fibers and activation of efferent fibers to the striated urethral sphincter, all of which inhibit detrusor activity through spinal inhibitory interneurons [17]. Increased amplitude of long latency somatosensory evoked potentials have been observed following PTNS treatment, suggesting possible plastic reorganisation of cortical network (cortical excitability) and long term potentiation [18].

It is uncertain whether the benefits of PTNS extend to a larger cohort of neurological patients reporting OAB symptoms, and whether outcomes differ from patients with idiopathic OAB. The objective of this study was to, therefore, evaluate the efficacy, safety and impact on quality of life (QoL) of PTNS in patients with and without neurological disorder reporting OAB symptoms.

Methods

This is a retrospective audit evaluating a PTNS service organised in an outpatients setting at a tertiary healthcare centre over an 18 month period. This open-label service evaluation was approved and registered with the Queen Square Division Quality and Clinical Governance Department. Consecutive patients with OAB symptoms refractory to first line conservative treatments, finding them either ineffective or intolerable, regardless of underlying diagnosis were offered PTNS treatment (Urgent PC, Uroplasty, Minnetonka, USA) [7]. All the patients were examined to confirm there was no underlying neurological or other condition in idiopathic OAB group. Patients were excluded from the treatment if they were unable to commit to attending weekly appointments, or diagnosed to have a urinary tract infection. Once PTNS treatment was started patients were instructed to maintain a stable dosage of the oral agent (antimuscarinic/ beta-3 adrenergic receptor agonist) during the 12 weeks course of treatment. The standard protocol includes 12 once weekly, 30 minute sessions, whereby the tibial nerve was stimulated with a 4 gauge needle inserted at a 60 degree angle approximately 5 cm cephalad to the medial malleolus and slightly posterior to the tibia at a frequency of 20 Hz and pulse width of 200 μsec [19]. Amplitude of stimulation ranged between 0.5 to 9 mA, being set at a comfortable level, based on an individual subject's foot and plantar motor response (flexion of big toe or fanning of toes) or sensory response (paraesthesias over the sole of foot) [7,20]. The primary outcome of this study was to evaluate the change in symptom score after 12 weeks of treatment for each group, idiopathic and neurogenic OAB, using questionnaire captured data and 3-day bladder diaries. Patients were asked to complete questionnaires and 3-day bladder diaries prior to treatment, and again after 12 sessions of treatment. Changes in OAB symptoms and LUT related QoL were assessed using the validated International Consultation on Incontinence Questionnaires (ICIQ): ICIQ-OAB and ICIQ-LUTSqol [21-24]. ICIQ-OAB is a 4-item questionnaire enquiring about urgency, frequency, nocturia, urgency leakage (score 0-16, higher score indicating worse symptom), and ICIQ-LUTS-qol evaluates LUT symptoms-related quality of life (score 0-76, higher score indicating worse impairment). The three-day bladder diary provides a real-time insight into urinary frequency (day and night), urgency, urinary leakage (with severity grading). Using the bladder diary, mean bladder urge was assessed using the Urgency Perception Score [25]. Bladder leakage severity was assessed using a subjective scale: 0 - none, 1 - mild, 2 - moderate, 3 - severe leakage. Satisfaction Survey administered at week 12 at the end of treatment was used to measure patient satisfaction and request to continue with the additional treatments after completion of 12-weeks (Supplementary Material 1). Patients who responded to treatment, as determined by the Satisfaction Survey administered at week 12 were invited to attend "top-up" maintenance treatments consisting of single session stimulation whenever symptoms began to wear off based upon self-reported recurrence of OAB symptoms. Patients were reviewed weekly by a nurse specialist. Any adverse events were documented by the treating team.

The change in the ICIQ-OAB and ICIQ-LUTSqol questionnaire scores, and the 3-day bladder diary parameters over twelve weeks of treatment was the primary outcome. Secondary outcomes were patient satisfaction and request to continue with the treatment, as measured by a more subjective Satisfaction Survey administered at the end of treatment at week-12. Sub-analyses were performed to identify the factors that could predict which patients would opt for “top-up” maintenance treatment. Idiopathic and neurogenic groups of patients were also compared for any difference in response to PTNS.

Differences in questionnaire scores and bladder diary parameters between baseline and week 12 were analysed and differences in response between patients with and without neurological disease were compared using paired t-tests. The distribution of continuous variables was examined and t-test, ANOVA, Kruskal Wallis test and Mann Whitney U test were applied as appropriate. Data analysis was done using Stata 13.1. All statistical test were two-sided and a p-value<0.05 was considered to be significant.

Results

Of 74 consecutive patients (52 women, 22 men; mean age (95% CI) 56.0 (52.2, 59.8) years) forty-nine (66.2%) patients had neurological disorder (19 (25.7%) multiple sclerosis (MS) and 30 (40.5%) other neurological conditions) and 25 (33.8%) idiopathic OAB (Table 1). Sixty-four (86%) patients completed 12 weeks of treatment (Figure 1).

Patients lost to follow-up discontinued treatment because of delayed improvement to first and second line treatments (n=2), no improvements in symptoms (n=2), inability to commit to weekly sessions (n=1) and adverse events (n=2) (pain, palpitations). The reason for discontinuing could not be established in 3 patients.

Patients with neurogenic OAB symptoms were comparable with regard to age, gender and baseline OAB severity to patients with idiopathic OAB at baseline (Table 2). No significant adverse effects were reported. Five patients reported mild discomfort at the site of needle insertion, however, this did not affect compliance to treatment.

Overall for the entire cohort significant improvements were recorded after 12 weeks of treatment in ICIQ-OAB total score, ICIQ-LUTSqol, change in 24h urinary frequency and mean number of incontinence episodes on bladder diary (Figure 2). In the neurogenic OAB group, there were statistically significant improvements in ICIQ-OAB total score and ICIQ-LUTSqol (Table 3).

There were no significant differences in outcomes between patients with idiopathic and neurogenic OAB (Table 3). Outcomes between the groups and absolute changes in key parameters are presented in detail in Supplementary Material 2. At the end of 12 weeks of treatment, 35 out of the 53 patients who had completed the Satisfaction Survey (66%) indicated a preference to continue with follow-up top-up maintenance treatment.

The mean top-up maintenance treatment interval was 44.4 days (range 7-155 days), with a mean top up frequency of 1.1 top ups/month. Factors predicting attending top-up maintenance treatment sessions were OAB symptoms (change per 1 unit increase on ICIQ-OAB, odds ratio (95% CI) 0.93 (0.87, 0.99), p=0.03), leakage severity (change per 1 unit increase on bladder diary, odds ratio (95% CI) 0.05 (0.01, 0.63), p=0.02) and QoL (change per 1 unit increase on ICIQLUTS-QoL, odds ratio (95% CI) 0.98 (0.96, 0.99), p=0.007) at week 12. Patients with a diagnosis of MS were more likely to return for top-up maintenance treatment (odds ratio (95% CI) 2.92 (0.85, 10.09), p=0.01), compared to other neurological patients and idiopathic group.

Discussion

Little is known about the outcomes of PTNS treatment in patients with neurological disorder. Phase 3 clinical trials evaluating PTNS for the management of OAB symptoms excluded neurological patients and therefore the benefits of treatment in this group is uncertain [7]. A few case series of patients with specific neurological diagnoses undergoing PTNS have been reported so far. These studies, predominantly in patients with MS, have demonstrated improvements in OAB symptoms following percutaneous and transcutaneous tibial nerve stimulation [26,7,17,14,27]. The mix of patients attending our clinic, therefore, provided a unique opportunity to assess differences between patients with and without neurological disease reporting OAB symptoms. Patients with idiopathic OAB and those with neurological disorder were similar in regard to their demographic characteristics and OAB symptom severity, and therefore the two groups were comparable. The pathophysiology of LUT dysfunction and OAB differs between groups and amongst neurological patients. Patients with a suprapontine lesion, such as PD and stroke, develop OAB due to uninhibited detrusor contractions, whereas patients with a spinal cord lesion, such as transverse myelitis and traumatic spinal cord injury, develop OAB due to the emergence of previously dormant C-fibre mediated reflex detrusor contractions at the level of the spinal cord [28,29]. On the other hand, the cause for LUT dysfunction in patients with idiopathic OAB is uncertain and myogenic, urothelial and occult neurogenic mechanisms have been hypothesised [30]. Importantly, no significant side effects were noted in either group.

Though there was a significant improvement in bladder diary and questionnaire scores in the group as a whole, only patients with neurological disease showed a significant improvement. This is contrary to the findings from previous studies [31,7] and could possibly reflect small sample size and lack of statistical power. The study was not specifically designed to compare idiopathic and neurogenic OAB and therefore though there is a suggestion that the outcomes of PTNS are more favourable in patients with neurogenic OAB, a randomised controlled study designed to compare the neurogenic and idiopathic OAB groups is required to properly evaluate differences in response between these two different groups.

High-level evidence supports the use of PTNS in the management of idiopathic OAB [7], and the results of this study seem to suggest that the outcomes of this treatment for neurogenic OAB are similar, without safety concerns. This is of significance as OAB symptoms are commonly reported in neurological patients, with a significant impact on QoL [29].

However this group of patients with neurological conditions, are all of low risk of upper urinary tract deterioration, and therefore these conclusions may not be applied to higher risk patient groups such as those with spinal cord injury and spina bifida [29].

The NICE guidance recommends PTNS as a second line treatment after oral agents, however, the position of PTNS in the treatment algorithm would be best informed by a direct comparative trials between PTNS and established treatments for OAB such as botulinum toxin [8]. Head to head studies of PTNS versus other treatment methods could be conducted, as PTNS is emerging to be the more economical and least invasive form of therapy.

Compared to the results of the SUmiT trial [7], where 55% of patients self-reported moderate to markedly improved symptoms, in this study 66% of patients felt that improvement in symptoms was significant enough to warrant attendance for further continuation therapy. This is in line with the results from a recent systematic review evaluating PTNS for the OAB, which suggested that around 50% of patients are 'successfully treated' [32,33].

The limitations of this study include the lack of blinding, and the lack of placebo or comparison arm,

as well as lack of urodynamic evaluation of patients before treatment. Urodynamic evaluation would provide further diagnostic information for this group of patients, however, in the clinical guidance, it is not a mandatory investigation before planning treatment [34]. Another limitations was that the questionnaires used were not validated in neurological patients.

After a 12-week course of PTNS, little is known about the long-term efficacy of top-up maintenance treatment. Symptoms recur after variable periods of time and on the average, this ranges between 6 weeks and 3 months [35,36]. The STEP study demonstrated at least 75% of patients reporting a positive response to the first 12 weeks of therapy, went on to have sustained symptom improvements up to three years, with an average top-up maintenance treatment once every 1.1 months [19].

The study suggests that PTNS is likely to be safe and effective for patients with OAB, however, a properly designed study including a control group is required to evaluate safety and efficacy in neurological patients.

Conclusions

PTNS appears to be a possible promising alternative for patients with neurological disorder reporting OAB who find first line treatments either ineffective or intolerable. However, a properly designed study is required to address safety and efficacy.

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Table 1. Underlying diagnosis of patients undergoing PTNS (n=74)

Diagnosis	**Number of patients**
Multiple sclerosis and demyelinating disorders	19
Parkinson's disease and parkinsonian disorders	7
Fowler's syndrome	4
Adrenomyeloneuropathy	4
Pure autonomic failure	1
Familial dysautonomia	1
Neurodegenerative ataxia	4
Epilepsy	2
Other neurological diagnoses (Myasthenia gravis, Alpha-actin deficiency, Systemic lupus erythematosus with cerebral involvement, poliomyelitis, limbic encephalitis, cauda equina syndrome, and cervical stenosis)	7

No known neurological or urological cause for OAB (idiopathic OAB)	25
Total	74

PTNS: percutaneous tibial nerve stimulation, OAB: overactive bladder

Table 2. Baseline characteristics showing no significant difference between patients with idiopathic and neurogenic OAB

	Entire cohort (N=74)	**Idiopathic OAB (N=25 (33.8%))**	**Neurogenic OAB (N=49 (66.2%))**	**p-value**
Gender; n male (%)	22 (29.7%)	6 (24.0%)	16 (32.7%)	0.74
Age; mean (SD)	56.0 (16.1)	58.3 (17.1)	53.7 (15.1)	0.65
ICIQ-OAB total score; mean (SD)	40.4 (9.8)	41.1 (11.6)	40.2 (8.9)	0.91
ICIQ-LUTSqol total score; Mean (SD)	186.9 (48.5)	186.9 (53.0)	187.6 (49.5)	0.97
24h urinary frequency (BD); Mean (SD)	11.3 (3.9)	12.6 (4.1)	10.8 (3.8)	0.39
Mean bladder urge (BD) score; Mean (SD)	2.4 (1.0)	2.6 (1.3)	2.3 (0.9)	0.30
Number of incontinent episodes (BD); mean (SD)	3.2 (4.4)	3.5 (5.9)	3 (3.8)	0.57

BD: Bladder diary, SD: Standard deviation, ICIQ: International Consultation on Incontinence Questionnaire, LUTS: Lower urinary tract symptoms, qol- Quality of life, OAB: Overactive bladder, PTNS: percutaneous tibial nerve stimulation

Table 3. Improvement in questionnaire and bladder diary parameters after 12 sessions of PTNS treatment showing significant improvement in cohort of patients with OAB

	Entire cohort	**Idiopathic OAB**	**Neurogenic OAB**	**p-value (Improvement in symptoms: Idiopathic vs. neurogenic OAB)**
Change in ICIQ-OAB total score; median (IQR)	-3 (-11.5, 5) (p=0.01)	-5.5 (-19, 3.5) p=0.2	-4 (-9.3, 2.5) p=0.04	0.19
Change in ICIQ-LUTSqol total score; median (IQR)	-16 (-57, 6.5) (p=0.004)	-16 (-62, 18) p=0.4	-34 (-53, 4.8) p=0.05	0.35
Change in 24h urinary frequency (BD); median (IQR)	-1.67 (-3.0, 0.33) (p=0.002)	-1.7 (-3.7, 0.3) p=0.4	-0.85 (-2.8, 0.4) p=0.3	0.50
Change in mean bladder urge score (BD); median (IQR)	-0.0 (-0.61, 0.13) (p=0.14)	-0.3 (-1.1, 0.1) p=0.6	0 (-0.4, 0.2) p=0.9	0.35
Change in mean number of incontinence episodes (BD); median (IQR)	-0.0 (-1, 0) (p=0.01)	-0.7 (-3, 0) p=0.8	-0.2 (-1, 0.2) p=0.8	0.36

BD: Bladder diary, IQR: Inter-quartile range, ICIQ: International Consultation on Incontinence Questionnaire, LUTS: Lower urinary tract symptoms, qol-Quality of life, OAB: Overactive bladder, PTNS: percutaneous tibial nerve stimulation

Figure 1. Flow chart of 74 patients undergoing PTNS treatment over an 18 month period

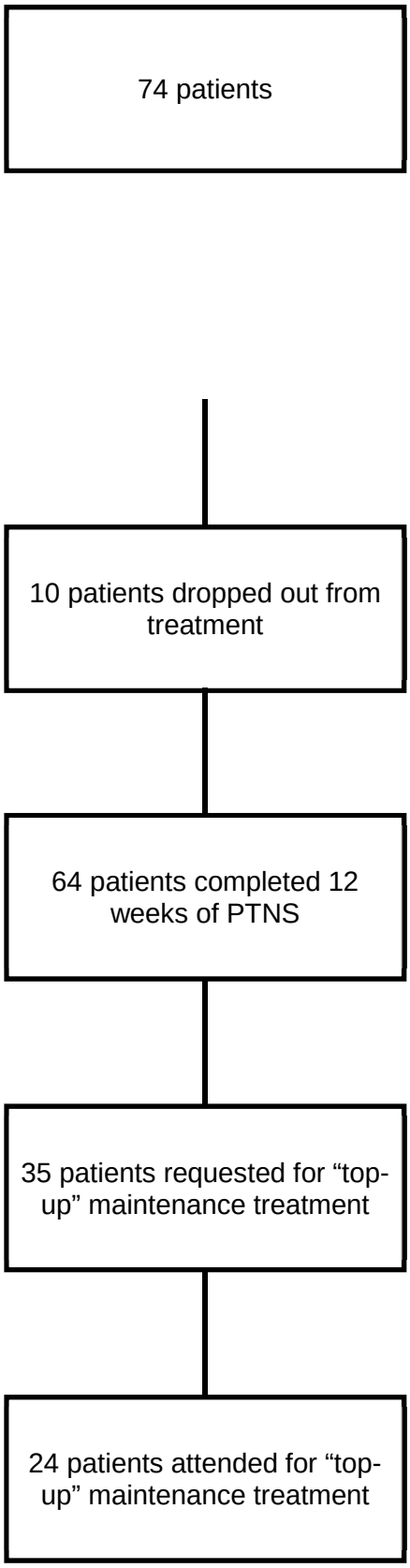

Figure 2. Values at baseline and at week 12 to visually depict the change in scores