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CLINICAL PAPER

Effectiveness of bilateral percutaneous posterior tibial nerve stimulation for women with idiopathic overactive bladder

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Abstract

Percutaneous posterior tibial nerve stimulation (PTNS) is an effective treatment for overactive bladder (OAB), but it is usually performed unilaterally. The aim of this study was to determine the effectiveness of a bilateral approach in women with OAB. The research took the form of a prospective cohort study of women with idiopathic OAB who received weekly bilateral percutaneous PTNS for 12 weeks. The participants completed the Overactive Bladder Questionnaire (OAB-q) and a 3-day bladder diary before and after treatment. The primary outcomes were changes in symptom severity and quality of life (QoL), as assessed using the OAB-q. The secondary outcomes included changes in bladder diary variables. Changes in the values of the outcome measures were assessed before and after treatment using a paired *t*-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed findings. Forty-two consecutive women were included in the study. The mean severity of symptoms reduced from 66.79 ± 17.71 at baseline to 39.88 ± 23.51 at a 12-week follow-up ($P < 0.001$). The mean improvement from baseline in the QoL scores was 24.63 ± 23.92 ($P < 0.001$). There was a statistically and clinically significant improvement in all the bladder diary parameters that were investigated. The results seem to compare favourably with existing data from unilateral PTNS studies. No serious adverse events occurred. The study found that bilateral percutaneous PTNS is an effective short-term treatment for women with OAB. A methodologically robust comparative study is warranted in order to determine whether bilateral PTNS achieves better clinical outcomes than the unilateral approach.

Keywords: detrusor overactivity, peripheral neuromodulation, urge incontinence, urinary urgency.

Introduction

Percutaneous posterior tibial nerve stimulation (PTNS) is a peripheral neuromodulation technique that involves electrical stimulation of the tibial nerve just above the medial malleolus. It is indicated for the treatment of overactive bladder (OAB). Percutaneous PTNS aims to stimulate the sacral nerve plexus (S2–4 roots), where the parasympathetic innervation of the bladder originates, through the afferent fibres of the tibial nerve, a mixed nerve containing L5–S3 fibres. This is achieved by inserting a needle electrode 3–5 cm cephalad to the medial malleolus. Electrical stimulation of the tibial nerve can also be performed with transcutaneous surface electrodes (transcutaneous PTNS).

Two systematic reviews of PTNS for OAB have reported similar levels of effectiveness (Burton *et al.* 2012; Wibisono & Rahardjo 2015). Wibisono & Rahardjo (2015), who included 11 randomized controlled trials (RCTs) and five prospective non-comparative studies involving

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a total of 787 adult participants, found that its effectiveness ranged from 37.3% to 81.8%. Burton *et al.* (2012) included two RCTs and 10 prospective non-randomized studies, and reported success rates ranging from 37% to 82%. In their meta-analysis, the pooled subjective and objective success rates were 61.4% [95% confidence interval (CI) = 57.5–71.8] and 60.6% (95% CI = 49.2–74.7), respectively.

Traditionally, percutaneous PTNS is performed unilaterally. However, a study has suggested that bilateral peripheral neuromodulation may activate a greater number of afferent sensory pathways, which could lead to an increase in effectiveness (Thomas *et al.* 2013a). To the present authors' knowledge, only two studies have investigated this theory, one on faecal incontinence (FI) (Thomas *et al.* 2013b) and another on anorectal pain (Takano & Arakawa 2016). Neither study involved patients with OAB.

The aim of the present study was to determine the effectiveness of bilateral percutaneous PTNS in women with OAB.

Participants and methods

The methods, definitions and units employed by the present authors conform to the standards jointly recommended by the International Urogynecological Association (IUGA) and the International Continence Society (ICS) (Haylen *et al.* 2010), except where specifically noted.

This was a prospective cohort study of women with symptoms of OAB who were treated with bilateral percutaneous PTNS from February 2014 to June 2015. The inclusion criteria were: women with a diagnosis of idiopathic OAB according to the current definition by IUGA and ICS (Haylen *et al.* 2010) who were 18 years of age or older, and had not adequately improved after conservative management, including lifestyle advice, bladder training, pelvic floor muscle (PFM) training (PFMT) and/or medication (e.g. antimuscarinic agents and/or mirabegron). Any patients who were receiving PTNS treatment but had a previous history of surgery for stress urinary incontinence, and those affected by neurogenic lower urinary tract dysfunction or PFM dysfunction were excluded from the data analysis.

The participants underwent a full urogynaecological history, pelvic floor assessment and urine dipstick analysis. They completed a 3-day bladder diary and the Overactive Bladder Questionnaire (OAB-q) before and after treatment. The OAB-q is a 33-item, validated, condition-specific questionnaire that has been shown to have sound psychometric properties (Coyne *et al.* 2006a). Overactive Bladder Questionnaire severity scores range from 0 to 100, with higher values indicating more-serious symptoms; OAB-q health-related quality of life (HRQoL) scores also range from 0 to 100, with higher values indicating better QoL.

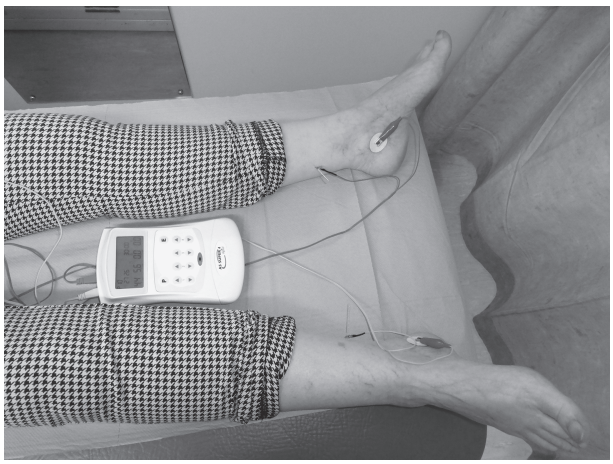

Figure 1. Position of the needles and surface electrodes.

Percutaneous PTNS was delivered bilaterally. Two, 40.0 × 0.2-mm (34-gauge) sterile acupuncture needles (Classic Plus, HMD Europe Ltd, Chipping Norton, Oxfordshire, UK) were inserted four finger-breadths cranial to each medial malleolus, and posterior to the medial border of the tibia. Self-adhesive skin electrodes were placed on the medial surface of the ipsilateral calcaneus tendon (Fig. 1). The stimulation was carried out with a low-voltage electrostimulator (AS Super 4 digital needle stimulator, Pierenkemper GmbH, Ehringshausen, Germany), which was set to a frequency of 20 Hz and a pulse duration of 200 μs in continuous mode. The amplitude (0–20 mA, adjustable in steps of 0.1 mA) was increased until flexion of the first toe or fanning of all toes was seen, or a tingling sensation in the sole of the foot was reported; stimulation was always at the highest tolerable level. Elevation of the intensity was allowed whenever the woman described fading of the above sensation as a result of accommodation. All participants received stimulation sessions that lasted for 30 min, and these were performed once a week for 12 weeks.

The primary end points of the study were changes in OAB-q symptom severity and HRQoL scores. The secondary outcomes included changes in urinary frequency and urgency, and episodes

of urgency incontinence, as determined by the 3-day bladder diary.

Statistical analyses

An *a priori* power analysis of a pre-/post-treatment design indicated that complete data for a sample size of $n = 34$ would be needed to achieve 80% power for a medium-sized effect (Cohen's $d = 0.5$, paired-samples t-test, $\alpha = 0.05$, $1 - \beta = 0.8$, two-sided). For this sample size of $n = 34$, power increases to 99% for a large effect size (Cohen's $d = 0.8$).

Statistical analysis was performed using the SPSS Statistics software package (IBM SPSS Statistics, Version 22.0, IBM, Armonk, NY, USA). Data distribution was evaluated using the Shapiro–Wilk test for continuous variables. Changes in OAB-q scores over time were analysed using paired-sample t-tests, and the effect size was calculated using Cohen's d, where $d < 0.1$ indicates a trivial effect, $0.1 < d < 0.3$ a small effect, $0.3 < d < 0.5$ a moderate effect, $0.5 < d < 0.8$ a medium effect, $0.8 < d < 1.3$ a large effect, and $d > 1.3$ indicates a very large effect. Pre- and post-procedure changes in the median values of bladder diary variables were assessed using the Wilcoxon signed-rank test. The effect size for this test is given by a correlation coefficient (r), which was calculated by dividing the z-value by the square root of N (N = number of observations over the two time points) (Pallant 2007). Effect size (r) values lie between 0 (no effect) and 1 (perfect effect), where $0 < r < 0.1$ is classified as no effect, $0.1 < r < 0.3$ indicates a small effect, $0.3 < r < 0.5$ a medium effect, and $r > 0.5$ indicates a large effect.

The present study was appraised by the local research and development committee, who deemed it exempt from ethics committee approval because it involved a review of anonymized data that were routinely collected in clinical practice in the present authors' unit. The study complies with the STROBE Statement (von Elm *et al.* 2008).

Table 1. Demographic data for the participants ($n = 42$): (SD) standard deviation

Variable	Result
Baseline characteristics (mean ± SD):	
age (years)	59.35 ± 11.54
body mass index (kg m^{-2})	31.42 ± 8.03
parity	2.33 ± 1.43
Type of lower urinary tract symptoms [*n* (%)]:	
overactive bladder:	
dry	3 (7.1%)
wet	14 (33.3%)
mixed urinary incontinence	25 (59.5%)
Urodynamic investigations [*n* (%)]:	
none	17 (40.5%)
investigations:	25 (59.5%)
detrusor overactivity	16 (64%)
no detrusor overactivity	9 (36%)

Results

Forty-two women who underwent bilateral percutaneous PTNS between February 2014 and June 2015 were included in the present study. The mean age [± standard deviation (SD)] of the participants was 59.3 ± 11.5 years, and their mean (± SD) body mass index was 31.42 ± 8.03. Their demographic and baseline characteristics are presented in Table 1.

Table 2 shows the summary statistics for the OAB-q severity and HRQoL scores. Thirty-eight of the 42 subjects (90.5% of the sample) showed a reduction in symptom severity. The mean (± SD) perceived severity of symptoms was significantly lower at 12 weeks (39.88 ± 23.51) than at baseline (66.79 ± 17.71) ($P < 0.001$). This reduction represents a large and clinically significant intervention effect (Cohen's $d = 1.29$). The mean increase in HRQoL score (24.63 ± 23.92) was also statistically and clinically significant ($P < 0.001$, $d = 0.99$). Overall, 81% of the sample (34 out of 42) reported both an improvement in HRQoL and a reduction in symptom severity.

The statistics for the secondary outcome data are presented in Table 3. All bladder diary

Table 2. Overactive Bladder Questionnaire health-related quality of life and symptom severity scores ($n = 42$): (SD) standard deviation; and (95% CI) 95% confidence interval

Measure	Mean ± SD (95% CI)	Significance	Cohen's *d*
Health-related quality of life:			
pre-treatment	37.90 ± 24.39 (30.30–45.50)		
post-treatment	62.54 ± 25.28 (54.66–70.42		
change	24.63 ± 23.92 (17.18–32.09)	$P < 0.001$	0.99
Symptom severity:			
pre-treatment	66.79 ± 17.71 (61.27–72.31)		
post-treatment	39.88 ± 23.51 (32.55–47.20)		
change	–26.91 ± 21.50 (20.21–33.61)	$P < 0.001$	1.29

Table 3. Bladder diary data (secondary outcomes) ($n = 42$): (IQR) interquartile range

Measure	Median	IQR	Percentile		Significance	Effect size (r)
			Twenty-fifth	Seventy-fifth		
Urinary frequency:						
pre-treatment	11.3	4.6	9.0	13.6		
post-treatment	8.6	3.8	6.6	10.5		
median difference	–3.0	1.6			$P < 0.001$	0.55
Urgency episodes:						
pre-treatment	5.1	4.3	3.0	7.3		
post-treatment	2.0	3.3	0.6	4.0		
median difference	–2.1	4.1			$P < 0.001$	0.41
Urge urinary incontinence:						
pre-treatment	2.5	4.0	0.5	4.6		
post-treatment	0.6	1.8	0.0	1.8		
median difference	–1.6	3.5			$P < 0.001$	0.42

parameters were significantly improved from baseline. The median number of micturitions in 24 h (± SD) decreased from 11.3 ± 4.6 at baseline to 8.6 ± 3.8 at the 12-week follow-up ($P < 0.001$). The number of episodes of urinary urgency per day (± SD) decreased from a median of 5.1 ± 4.3 to 2.0 ± 3.3 ($P < 0.001$). The median number of urge incontinence episodes also reduced from 2.5 (4.0) to 0.6 (1.8) ($P < 0.001$). These changes in bladder symptoms were also clinically significant, with the larger effect being observed in the reduction in the number of episodes of micturition in 24 h.

Two episodes of minor bleeding at the needle site were observed in two women after the fourth and tenth sessions, respectively. Two participants reported moderate pain/discomfort during the insertion of the needles at their first and fifth sessions, respectively. One subject complained of lower-leg tightness lasting for 24 h, and another described temporary mild swelling of her left ankle; both incidents occurred after their initial PTNS sessions. These adverse effects were very mild, and did not result in any participant discontinuing treatment.

Discussion

The present study shows that bilateral percutaneous PTNS is effective in the treatment of female idiopathic OAB. The majority of participants met the minimum important difference (MID) for changes in OAB-q scores for both symptom severity and HRQoL. The MID has been defined as a score change that reflects a clinically meaningful response to treatment (Coyne *et al.* 2006b; Dyer *et al.* 2011). For the OAB-q instrument, the MID has been found to be a reduction of between –13 and –25 in symptom severity, and an increase of between +5 and +12 in HRQoL scores (Dyer *et al.* 2011). The mean changes in these scores (± SD) in the present study were –26.9 ± 21.5 and +24.6 ± 23.9, respectively, indicating a statistically and clinically significant improvement in subjectively reported outcomes.

Unilateral PTNS has been investigated in several observational studies and some RCTs, which have compared it to either sham treatment or antimuscarinic agents (Karademir *et al.* 2005; Peters *et al.* 2009, 2010; Finazzi-Agrò *et al.* 2010; Sancaktar *et al.* 2010; Preyer *et al.* 2015). Peters *et al.* (2009, 2010) reported mean reductions (± SD) in the number of micturitions per 24 h of 2.4 ± 4.0 and 2.4 ± 2.5, respectively, after 12 weeks of treatment with unilateral PTNS. More recently, Preyer *et al.* (2015) found a non-significant change in the mean number of micturitions (± SD) before (11.3 ± 3.0) and after (10.3 ± 4.0) 12 PTNS sessions in an RCT comparing PTNS with tolterodine.

The present data seem to compare favourably with the existing literature. In this study, the median (interquartile range) of differences in urinary frequency after the intervention was –3.0 (1.6). Furthermore, the median reduction in urge incontinence episodes in this study was –1.6. Peters *et al.* (2010) reported a median change in episodes of urge urinary incontinence of –1.3, while the mean change from baseline in these authors' previous study was –1.0 ± 2.2 (Peters *et al.* 2009).

It has been argued that bilateral peripheral neuromodulation may activate a greater number of afferent sensory pathways, which could lead to an increase in effectiveness (Thomas *et al.* 2013a). However, very few published studies have investigated bilateral peripheral neuromodulation. In a small, observational paper, Thomas *et al.* (2013b) reported better short-term clinical outcomes in the management of FI using daily

bilateral transcutaneous PTNS for 6 weeks than with the unilateral approach. Only one further study (Takano & Arakawa 2016) and a case report (Matzel *et al.* 2002) have been published on this topic. Takano & Arakawa (2016) investigated bilateral PTNS in the management of functional anorectal pain, while the case report refers to a case of bilateral sacral neuromodulation for FI following surgery for rectal cancer. To the present authors' knowledge, this is the first paper reporting the outcomes of bilateral percutaneous PTNS in women with OAB.

In the present study, 90.5% of the participants (38 of 42) reported an improvement in their symptoms. Moreover, 34 of 42 (81%) showed an improvement in both symptom severity and HRQoL. This also compares favourably with the figures reported in most of the literature for unilateral PTNS. The reported success rates for unilateral PTNS range from 37.3% to 81.8% (Wibisono & Rahardjo 2015), depending on the definition of the treatment response. However, the present authors cannot suggest that bilateral percutaneous PTNS is more effective than unilateral treatment since this study is observational and non-comparative.

The PTNS treatment was well tolerated, and there were no serious adverse events. The only occasional procedure-related adverse effects reported were minor bleeding and discomfort/pain at the needle site. However, these were very mild and did not cause any participant to discontinue treatment.

An important strength of the present study is the use of patient-reported outcome measures and a validated instrument (the OAB-q) for the assessment of symptom severity and HRQoL. The authors used a standardized percutaneous PTNS technique that had been described in that literature (Peters *et al.* 2009), but they used it on both legs simultaneously. The limitations of the present study include the small study sample, the lack of a control group and the short-term follow-up. However, an RCT is currently being conducted in the present authors' institution that compares long-term maintenance therapy with monthly bilateral PTNS sessions versus home-based bilateral transcutaneous PTNS. Women who responded to percutaneous PTNS in the present study have been invited to participate in the RCT, which will be reported in the near future.

In conclusion, bilateral percutaneous PTNS is an effective short-term treatment for women with OAB. A large, methodologically sound comparative study is warranted in order to determine whether bilateral stimulation produces better outcomes than unilateral PTNS in the treatment of women with idiopathic OAB symptoms.

Conflicts of interest

The authors declare that there were no conflicts of interest.

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