Efficacy of percutaneous posterior tibial nerve stimulation for the management of faecal incontinence in multiple sclerosis: a pilot study

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Abstract

Background

Faecal incontinence is a debilitating and highly prevalent problem among multiple sclerosis patients. Conservative therapies often fail to provide benefit. Posterior tibial nerve stimulation is a minimally invasive neuromodulatory therapy with proven efficacy for faecal incontinence in non-neurological settings.

Objective

To evaluate the efficacy of posterior tibial nerve stimulation in treating multiple sclerosis-related faecal incontinence.

Methods

Consecutive multiple sclerosis patients with faecal incontinence that had failed conservative therapy received posterior tibial nerve stimulation between 2012-2015. All patients had previously undergone anorectal physiology tests and endoanal ultrasound. Patients whose Wexner incontinence score reduced below 10 post-therapy or halved from baseline were deemed responders.

Results

Thirty-three patients (25 female, median age 43 years) were included. Twenty-three (70%) had urge, 4 (12%) passive and 9 (27%) mixed faecal incontinence. Twenty-six (79%) were classified as responders. The majority of subjects had

relapsing-remitting multiple sclerosis (67%); those had a significantly higher response rate (95% vs. 67% and 50% in primary and secondary progressive respectively, $P<0.05$). Responders tended to be more symptomatic at baseline and had greater improvements in bowel symptom scores and quality of life scores with therapy.

Conclusion

Posterior tibial nerve stimulation demonstrates potential as an effective therapy for faecal incontinence in multiple sclerosis. These findings provide the basis for future more definitive controlled studies.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system, which causes progressive disability as demyelinating lesions accumulate in the brain and spinal cord. The disease typically has onset in young adulthood, has a predilection for females and occurs most often in Western countries, where the prevalence is at least 100 per 100,000 persons.(1)

Abnormalities of bowel function, including both constipation and faecal incontinence (FI), are common in MS. FI is present in up to 50% of these patients, and frequently occurs along with constipation.(2, 3) The pathophysiology of FI in MS may be related to direct effects of the condition such as central nervous system lesions impairing afferent and efferent pathways to the bowel, impaired anorectal sensation or behavioural changes affecting toileting habits. Other global features of MS such as striated muscle weakness and impaired mobility may also play a role.(2)

Management of FI in MS remains empirical and is mostly similar to that offered to non-neurogenic FI patients. Conservative therapies are used first-line; these include dietary advice, stool bulking fiber supplements, anal plugs for containment and the use of anti-motility drugs such as loperamide. Our group has previously published on the efficacy of biofeedback and transanal irrigation in MS,(4, 5) but there is certainly a need for additional treatment options.

Posterior tibial nerve stimulation (PTNS) is a form of neuromodulation that has gained acceptance in the treatment of FI. A number of published studies have now demonstrated significant benefits from PTNS, however these studies either excluded patients with MS or included very few;(6, 7) hence it is unclear whether the findings can be extrapolated to the MS cohort. The mechanism of action of PTNS has not been fully elucidated, however modulation of central pathways regulating colorectal motility and afferent sensory perception probably plays a part.(8, 9) If so, then it is conceivable that PTNS would be of benefit in this patient group. The aim of the present study is to determine whether PTNS is effective in the treatment of FI in MS patients, and also to identify factors that predict treatment success as a pilot to plan a definitive randomized study.

Materials and methods

Study design

A retrospective analysis of prospectively collected data was performed. MS patients with FI were first treated with PTNS at University College London Hospital, a tertiary referral centre, in 2012; we included consecutive patients who underwent this treatment during a three-year period following this (i.e. between 2012 and 2015). Baseline characteristics including age, duration and type of MS, and obstetric history were ascertained. All subjects had previously failed conservative therapies including biofeedback, and had undergone anorectal physiology investigations and an endoanal ultrasound. Failure to regularly attend the scheduled PTNS sessions was the sole exclusion criterion.

PTNS

A protocol was used to provide a standardized procedure for the administration of PTNS to all study subjects.(7, 10) A 34 gauge needle was inserted 5cm cephalad to medial malleolus and 2 cm posterior to tibia at a 60° angle, with a base electrode placed on the ipsilateral leg, with the patient lying supine or sitting in a chair (Figure). Both electrodes were then connected to the neurostimulator device (Urgent PC, Cogentix, Manchester, UK). Correct needle placement was confirmed in all subjects by motor and/or sensory response (flexion of big toe, fanning of all toes or tingling sensation of foot extending to all toes). A suitable neurostimulation setting was then chosen whereby the patient was able to comfortably receive 30 minutes of therapy; subjects received neuromodulation therapy at this optimal setting on a weekly basis for a minimum of 8 weeks. If no response was obtained at 8 weeks then therapy was ceased, as per our unit policy given absence of subsequent treatment response in our experience. Those who had exhibited some response during the first 8 weeks continued therapy so that they completed 12 weeks in total.(11)

Anorectal physiology testing

Testing was performed using standardised methods that have been described elsewhere in detail; our previously reported normal values are used.(4, 12, 13) An 8-channel water perfused catheter (Ardmore Healthcare Limited, External Diameter 3.9 mm with Mui pump, using Medical Measurement System software) was used to determine anal resting and squeeze pressures by the “station pull-

through" method. Rectal sensitivity to mechanical sensation was measured by inflation of a latex balloon placed 6cm above the anal verge, with the threshold volume, urge volume (where urge to defecate is first perceived) and maximal tolerated volume all being ascertained. Lastly, anal and rectal sensitivity to electrical sensitivity were measured using a bipolar electrode catheter (GaeltecLtd, using Medical Measurement System software). Electrical stimulation was applied to the anus (at 1cm above the anal verge), followed by the rectum (at 6cm above the anal verge). In the anus, stimulation was applied at 5 Hz with a pulse width of 0.1 ms, and the current gradually increased to 20 mA until the patient first reported sensation. The same process was repeated in the rectum using 10 Hz, pulse width 0.5 ms, and gradual increase of current up to 50 mA.(14)

Endoanal ultrasound

Ultrasound examination was performed by experienced radiologists in the established fashion.(15, 16) Briefly, the endoanal ultrasound probe (BK Medical Profocus, Herley, Denmark) was inserted into the rectum with the patient in the left lateral decubitus position. Contiguous images of the anal sphincter were captured, from its proximal extent at the puborectalis muscle and proceeding caudally. Hyper- or hypoechoic disruptions in the internal and/or external anal sphincters of at least 5mm thickness were noted.

Outcomes

At baseline and immediately following completion of PTNS therapy, a number of validated measures of symptom severity in patients with FI were administered and the results collected. These included:

- The Wexner Incontinence questionnaire is a validated and reproducible measure for assessing severity of faecal incontinence; it does so on a scale of 0 to 20, with 0 representing the absence of any symptoms and 20 corresponding to the greatest severity of symptoms.(17)
- The Rockwood score is a reliable and valid quality of life measure specific to faecal incontinence.(18) It assigns a score for each of 4 domains, lifestyle, coping, depression and embarrassment. These are scored between 1 and 5, with 1 indicating lower functional status or quality of life.
- Two visual analogue scales (VAS) were used, for bowel and bladder symptoms respectively. Each produced a score between 0 and 100, with a higher score corresponding to a greater severity of symptoms within that system.
- The Bristol Stool Form Scale has not been validated for use specifically in FI, but is a valid and reliable 7-point scale used extensively in clinical and research settings for measurement of stool form in both healthy patients and those with diarrhea.(19) Type 1 stools are excessively hard and dry whereas Type 7 are the most watery. Type 3 and 4 are normal stools.

We chose to analyse all of the patients as a single cohort. Outcome was assessed on the basis of response to treatment. Subjects were classified as responders or

non-responders to the treatment based on reduction in Wexner score to below 10 or by halving of the baseline score, as has been used in previous studies.(20-22) Characteristics of responders and non-responders were then compared in order to identify factors potentially predictive of response to therapy.

Statistics

Statistical analysis was undertaken using Microsoft Excel and STATA. For normally distributed data, paired two-tailed t-tests were used. For non-parametric data Mann-Whitney U tests were used. For parametric data, Pearson correlation was used. Chi-squared and its other variants (i.e. Fisher tests) analysed non-parametric data. A p-value of ≤ 0.05 was considered significant.

Results

Demographics

A total of 33 patients (25 female) fulfilled the criteria and were included in the study. The median age was 48 years (IQR: 41-58 years). Median time since diagnosis of MS was 14 years (9-26 years), while median duration of FI symptoms was 10 years (6-13 years). 22 patients (67%) had relapsing-remitting MS, 3 (9%) had primary progressive MS and 8 (24%) had secondary progressive MS. Anal canal length was within the normal range (between 2 – 4.5cm) in 32 out of 33 patients.

The vast majority (29 patients, 88%) gave a history of urge FI; of these nine (27%) also described passive FI along with urge symptoms, while only four patients (12%) had purely passive FI. Three patients were already taking loperamide and glycerine suppositories, two were taking an osmotic laxative, one was taking a stimulant laxative and one was taking hyoscine butylbromide; these were continued during the study period. Otherwise, the majority of patients (79%) were not concurrently taking any laxatives or drugs affecting gastrointestinal motility.

Patients were followed until the end of their treatment duration. 26 patients (79%) were classified as responders by the predetermined Wexner score criteria, while 7 (21%) were non-responders. In magnitude, mean Wexner score among responders reduced from 13.5 ± 3.8 at baseline to 7.0 ± 2.8 after PTNS therapy, whereas in non-responders it rose slightly from 13.4 ± 3.9 to 13.9 ± 3.1 (Table 1). There was no significant difference in age between responders and non-responders (P=0.36).

Change in symptom outcome measures in responders and non-responders

A comparison of VAS, Rockwood and Bristol Stool scores pre- and post- PTNS is displayed in Table 2. At baseline responders tended to be more disabled as measured by most of these outcome scores, being significantly more so by the Rockwood depression subscore. Responders demonstrated improvement in at least some objective outcome measures related to their FI; on the other hand non-

responders did not demonstrate any significant improvement in any parameters, and in fact exhibited worsening in most of these outcomes. Responders demonstrated an improvement in the Rockwood depression score (2.7 ± 0.8 pre to 3.1 ± 0.9 post therapy, P=0.01). In addition, we observed that responders exhibited an improvement in stool consistency following treatment, as demonstrated by change in median Bristol Stool Form Scale score (from 5 to 4, P=0.02). When the magnitude of improvement in all parameters was compared between responders and non-responders, a trend towards greater improvement amongst responders was seen, though this only reached significance for the Rockwood depression score and the Bristol Stool Form score.

Factors associated with treatment success

Relapsing remitting MS subtype was associated with statistically greater likelihood of treatment response (P<0.05), with 95% in this subset reporting success in comparison to those with primary progressive (67%) and secondary progressive MS (50%).

Amongst the 25 female patients, 16 had had vaginal deliveries. Of these, the number of vaginal deliveries was not related to treatment outcome (P=0.61).

The majority of the cohort had ultrasonographically intact external and internal anal sphincters; with only 5 (16%) demonstrating defects in sphincter integrity or sphincter atrophy. Sphincter integrity was not associated with treatment outcome (P=0.94).

Comparing baseline anorectal physiology parameters between responders and non-responders, we found no statistically significant difference in resting and squeeze pressures, sensitivity to balloon distension or electrosensitivity between responders and non-responders (Table 3).

Discussion

The feasibility of PTNS for FI in two spinal injury patients has been previously described,(23) but the present study is the first to examine the efficacy of PTNS for FI amongst a cohort patients with MS. We report a high rate of treatment success in a carefully defined population. Improvement was seen in 81% of subjects who underwent therapy as defined by improvement in Wexner score. This is a higher rate of success than has been previously described in studies of PTNS for FI,(6) where those with neurologic causes were generally excluded or limited to one or two patients amongst the entire cohort.(24) The improvement in Wexner score in responders was accompanied by a trend to improvement in the bowel VAS score and quality of life scores, though this only reached significance for the depression subscore. These improvements are in keeping with the already recognised correlation between Wexner score and quality of life.(25)

We observed that patients who responded to PTNS tended to be more disabled at baseline, in terms of not only bowel symptoms but also quality of life. It may be that part of the reason for lack of benefit perceived in non-responders was due to lesser severity of symptoms at baseline. Alternatively, patients with greater

diability may have benefited from the intensive clinical follow up that is part of PTNS therapy.

The only factor we found that was predictive of treatment success was relapsing remitting MS subtype. While response rates for all subtypes were good, rates were significantly lower for secondary and primary progressive subtypes. Given current consensus on the clinical course of MS subtypes, our findings could be explained by a greater neurological disease burden in the progressive subtypes, meaning that any form of therapy is less likely to succeed;(26, 27) however, it must be noted that the number of patients with secondary and primary progressive MS was far lower than the number with relapsing-remitting.

Other factors we examined were not predictive of treatment success, with our findings being largely in keeping with those reported in previous studies of PTNS in non-neurogenic FI. Sphincter integrity was unrelated to treatment outcome, as has been demonstrated previously in non-neurogenic FI.(28) No anorectal physiology parameter was associated with treatment outcome; this is unsurprising, since it is known that efficacy of PTNS seems to derive from something other than changes measurable by standard anorectal physiology parameters.(7)

If not through changes in anorectal physiology, then how does PTNS improve faecal incontinence? Our findings are also of interest given they help to deepen our understanding of the mechanisms of action, which are still not precisely understood. PTNS probably acts in a number of ways, but the mechanism that is

most plausible is activation of somatic afferent fibres that, through activation of somato-visceral reflexes and modulation of sympathetic and parasympathetic neurons, inhibit colonic activity and enhance internal anal sphincter activity.(29) It is unclear whether this is via a spinal or supraspinal pathway; both may be involved. MS is a heterogeneous condition that can cause FI through a combination of factors, and one characterised by its very nature of having disseminated central nervous system lesions. Given that our cohort demonstrated a high rate of treatment success, across all subtypes, it fits in with the theory that PTNS works via activation of a number of somato-visceral reflexes, probably on both a spinal and supraspinal level.

Focusing in particular on the possibility that the efficacy of PTNS is mediated by its effects on colonic motility, we also found that responders to PTNS were characterised by a significant improvement in stool consistency, supporting that hypothesis. This is conceivable, since by peripherally stimulating the sacral spinal cord, PTNS could cause reductions in colorectal motility and increase in intestinal transit time in a similar fashion to that already demonstrated by sacral neuromodulation.(30, 31) Stool consistency is not an outcome that has been assessed in other trials of PTNS. Our findings lend support to the hypothesis that improvements in stool consistency secondary to inhibition of colonic motility underlies at least some of the clinical efficacy of PTNS.

We acknowledge the lack of a control group in our study and the consequent failure to account for placebo response. However, the admittedly high placebo response rates in other sham-controlled trials of percutaneous PTNS have never

been greater than around 30%, whether measured by reduction in FI episodes or by improvements in Wexner or quality of life scores.(7, 32) This implies that the effect size we described was more than could be attributed to a placebo effect. The data in this study provides the basis of a power calculation for a future definitive study. In addition, future studies could expand on our findings by examining long-term outcomes in this group of patients; we know that in non-neurogenic FI, durability of treatment response is reasonable, albeit often requiring 'top-up' PTNS sessions.(33, 34)

In conclusion, this is the first study to describe the efficacy of PTNS in MS-related FI. The cohort as a whole exhibited a very high rate of treatment response (81%), and those with relapsing-remitting subtype did even better. Our findings suggest that PTNS is an effective tool for these patients, and also sheds light on its mechanism of action.

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Table 1 – Wexner score changes in responders and non-responders to PTNS

	Responders	Non-responders
N (%)	26 (79%)	7 (21%)
Baseline Wexner score, mean ± SD	13.5 ± 3.8	13.4 ± 3.9
Post-therapy Wexner score, mean ± SD	7.0 ± 2.8	13.9 ± 3.1

Table 2 – Measures of symptom severity before and after treatment in responders and non-responders

	Responders			**Non-responders**			**Change in values**		
	Baseline	**After treatment**	***P***	**Baseline**	**After treatment**	***P***	**Responders**	**Non-responders**	***P***
Visual analogue scores									
Bowel	58.5 ± 25.4	52.3 ± 24.8	0.28	45.7 ± 22.8	46.4 ± 14.1	0.67	-6.2	+0.9	0.47
Bladder	51.0 ± 26.0	53.1 ± 23.2	0.69	52.9 ± 25.1	50.7 ± 20.1	0.74	+2.1	-2.2	0.91
Rockwood quality of life scores									
Life	2.5 ± 0.9	2.9 ± 0.8	0.11	3.2 ± 0.7	3.1 ± 0.9	0.01	+0.4	-0.1	0.25
Coping & Behaviour	2.0 ± 0.7	2.4 ± 0.9	0.15	2.6 ± 0.4	2.4 ± 0.8	0.15	+0.4	-0.2	0.20

Depression & Self Perception	2.7 ± 0.8*	3.1 ± 0.9	0.01	3.4 ± 0.4*	3.1 ± 0.8	0.18	+0.4	-0.3	0.05
Embarrass-ment	2.2 ± 0.8	2.6 ± 0.8	0.06	2.5 ± 1.0	2.4 ± 1.0	0.54	+0.4	-0.1	0.21
Bristol Stool Form score	5 (4-6)	4 (3-4)	0.02	5 (5-5.5)	5 (4.5-5.5)	0.44	-1	0	0.01

* $P<0.05$ for responders vs. non-responders baseline values; Higher visual analogue scores correspond to greater severity of symptoms; Lower Rockwood scores correspond to greater disability; Lower Bristol Stool Form scores correspond to firmer stool consistency; Values are means ± SD, medians (IQR)

Table 3 – Correlation of physiology parameters, patient and disease factors with treatment success

Outcome measure	**Responders (n=26)**	**Non-responders (n=6)**	***R***	***P***
Age, years	44.5 (36-57)	46 (41-56.5)	-0.08	0.66
Disease factors				
Duration of MS, years	14.5 (9-25)	14 (11-27.5)	0.01	0.99
Duration of GI symptoms, years	10 (6-13)	7 (6.5-13)	0.17	0.35
MS subtype	RR 20, PP 2, SP 4	RR 2, SP 4		<0.05
Other FI risk factors				
Number of vaginal deliveries	1 (0-2)	1 (1-3)		0.62
Intact sphincter, n (%)	22 (85%)	5 (83%)		0.94
Anorectal physiology parameters				
Resting pressure, mm Hg	76 ± 23	71 ± 30	-0.19	0.30

Squeeze pressure, mm Hg	51 ± 40	56 ± 57	0.09	0.62
Cough increment pressure, mm Hg	46 ± 20	64 ± 24	-0.06	0.74
Threshold volume, mL	37 ± 21	34 ± 14	-0.01	0.96
Urge volume, mL	86 ± 38	63 ± 51	-0.04	0.83
Maximum tolerated volume, mL	168 ± 61	129 ± 82	0.01	0.97
Anal sensory threshold, mA	11 ± 4	11 ± 6	0.14	0.77
Rectal sensory threshold, mA	23 ± 12	26 ± 14	0.05	0.55

MS, multiple sclerosis; FI, faecal incontinence, RR, relapsing remitting; PP, primary progressive; SP, secondary progressive; GI, gastrointestinal; Values are medians (IQR) and means ± SD

Figure

PTNS in use on a patient, demonstrating correct electrode placement and ability to adjust neurostimulation setting.