

Double-blind randomised controlled trial of percutaneous tibial nerve stimulation versus sham electrical stimulation in the treatment of faecal incontinence: **CONtrol of Faecal Incontinence using Distal Neuromodulation (the CONFIDeNT trial)**

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Scientific summary

The CONFIDeNT trial

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Scientific summary

Background

Faecal incontinence (FI) poses a significant UK public health problem, with an estimated prevalence of 11–15% among adults. It is known to be an under-reported problem that significantly impacts on quality of life. It often causes social and psychological disability, leading to stigmatisation and social exclusion.

Management of FI is challenging owing to a widespread lack of expertise, high prevalence and multiple aetiologies. Neuromodulation is a relatively new treatment modality for FI. It is based on recruitment of residual anorectal neuromuscular function pertinent to continence by electrical stimulation of the peripheral nerve supply, without the need for surgery to the anus itself.

Tibial nerve stimulation is a minimally invasive neuromodulatory modality. The tibial nerve contains afferent and efferent fibres originating from the fourth and fifth lumbar nerves and first, second and third sacral nerves. Thus, stimulation of the tibial nerve is thought to lead to improved continence in a similar way to sacral nerve stimulation but without the need for a permanent surgically implanted device. Tibial nerve stimulation is an outpatient treatment which can be delivered by any trained health-care professional. Two main delivery methods are described: percutaneous tibial nerve stimulation (PTNS) and transcutaneous tibial nerve stimulation (TTNS). The main perceived advantage of PTNS over TTNS is the proximity of the needle to the tibial nerve, enabling higher treatment amplitude to be delivered while avoiding the painful skin sensations associated with transcutaneous treatment.

Observational studies of PTNS have shown improvements in most outcome measures (bowel diary, Cleveland Clinic Incontinence Score and quality-of-life measures) after treatment, compared with baseline. A small three-arm RCT of PTNS versus TTNS versus sham showed effects of both treatments over sham, with PTNS appearing superior.

Percutaneous tibial nerve stimulation may offer a repeatable, low-cost (estimated at £5916 for the first 10 years based on 6-monthly top-up sessions) minimally invasive outpatient technique. It may, therefore, offer a genuinely new option in the pathway to treat FI.

Objectives

The aim of this study was to assess the clinical effect of PTNS compared with sham electrical stimulation in the treatment of patients with significant FI. Clinical outcomes, derived from bowel diaries and validated, investigator-administered questionnaires, were assessed at baseline and 2 weeks following a 12-week course of treatment. Outcomes were as follows.

Primary outcome

Responder versus non-responder, defined as a patient achieving $\geq 50\%$ reduction in faecal incontinence episodes (FIEs) per week.

Secondary outcomes

- Percentage change in FIEs per week (i.e. patients achieving $\geq 25\%$, $\geq 75\%$ or 100% reduction in weekly FIEs).
- Change in FIEs per week as a continuous measure.
- Change in symptom severity score: St Mark's Contingence Score (SMCS).
- Change in disease-specific quality-of-life scores:
 - Gastrointestinal Quality of Life Index
 - Faecal Incontinence Quality of Life Index.
- Change in generic health-related quality-of-life measures: Short Form Questionnaire-36 items.
- Change in patients' health status and overall health using European Quality of Life-5 Dimensions questionnaire.
- Change in a patient-centred outcomes visual analogue scale questionnaire.
- Likert scale of patients' global impression of success (scale of 0–10).
- Qualitative data:
 - patient-perceived impression of change in use of incontinence pads and constipating medications
 - patient-perceived impression of change in urinary symptoms
 - patient impression of the treatment in general
 - patient-perceived allocation (PTNS or sham).

Other outcomes recorded at each visit

- Stimulation parameters.
- Adverse events and concomitant medications.

Methods

This study was a UK-based multicentre, pragmatic, parallel-arm, double-blind, randomised controlled trial. There was equal allocation between the arms, with stratification by sex and centre.

Centres with specialist expertise in FI and adequate staffing (at least two staff members), which demonstrated expertise with PTNS, were invited to participate in the study. All adult patients with FI symptoms sufficiently severe to warrant intervention in whom appropriate conservative therapies had failed were invited to participate. Inclusion and exclusion criteria were as follows.

Inclusion criteria

- Faecal incontinence sufficiently severe to warrant intervention (as recommended by the principal investigator at each site).
- Failure of appropriate conservative therapies.
- Age ≥ 18 years.

Exclusion criteria

- Inability to provide informed consent for the research study.
- Inability to fill in the detailed bowel diaries required for outcome assessments (this excluded participants who do not speak/read English).
- Neurological diseases, such as diabetic neuropathy, multiple sclerosis and Parkinson's disease (including any participant with painful peripheral neuropathy).

- Anatomical limitations that would prevent successful placement of needle electrode.
- Other medical conditions precluding stimulation, for example bleeding disorders, certain cardiac pacemakers, peripheral vascular disease or ulcer, lower leg cellulitis.
- Congenital anorectal anomalies or absence of native rectum due to surgery.
- A cloacal defect.
- Present evidence of external full-thickness rectal prolapse.
- Previous rectal surgery (rectopexy/resection) done < 12 months previously (24 months for cancer).
- Stoma in situ.
- Chronic bowel diseases such as inflammatory bowel disease leading to chronic uncontrolled diarrhoea.
- Pregnancy or intention to become pregnant.
- Previous experience of sacral nerve stimulation or PTNS.

Each patient was scheduled to attend for 14 study visits, the first for eligibility checking, visits 2–13 for collection of baseline data followed by delivery of treatment (PTNS or sham) and the final study visit for the collection of outcome data. Participants who recorded zero incontinent episodes on initial bowel diary were not excluded from the study.

Percutaneous tibial nerve stimulation was delivered via the Urgent® PC device (Uroplasty Limited, Manchester, UK), a hand-held pulse generator unit, with single-use leads and fine needle electrodes. The needle was inserted near the tibial nerve on the right leg, adhering to the manufacturer's protocol (and specialist training). Treatment was for 30 minutes weekly for 12 treatments. Validated sham stimulation involved insertion of the urgent PC needle subcutaneously at the same site with electrical stimulation delivered to the distal foot using transcutaneous electrical nerve stimulation. Participants were blinded to treatment allocation, and all equipment was hidden from their view. Standard instructions were read to all participants prior to every treatment, with patient contact limited to questions regarding adverse events, concomitant medications, loperamide and incontinence pad usage in order to standardise treatment. To maintain treatment quality, each researcher underwent individual training on how to deliver PTNS and sham treatment, and technique was assessed at 6-monthly intervals.

Randomisation, with allocation concealment, was undertaken using a bespoke web-based computer program held at Nottingham Clinical Trials Unit. Following input of participant details, immediate on-screen randomisation occurred. Allocation was on a 1 : 1 basis, with initial stratification by sex and then, because the numbers of males was expected to be very small and we wanted to achieve an overall balance of males in each group, stratification of females only by centre.

Sample size calculation was based on an estimated PTNS treatment response of 55% and a sham response of 35%. Overall, 212 participants were required for the analysis with 80% power at the 5% significance level. Statistical analysis, on an intention-to-treat basis, was carried out using Stata version 12.1 (StataCorp LP, College Station, TX, USA), interfacing with Realcom Impute (2007, Centre for Multilevel Modelling, University of Bristol, Bristol, UK), which was used to multiply impute missing outcome and baseline covariate data. Per-protocol analysis, sensitivity analyses and subgroup analyses were subsequently performed.

Results

Eighteen UK centres recruited participants for the trial between 23 January 2012 and 31 October 2013. In total, 373 participants were screened and, of these, 227 (61%) were randomised. Of these, 115 participants were randomised to receive PTNS and 112 randomised to receive sham electrical stimulation. The number of participants per site ranged from 1 to 45 (median 10 patients). There were 12 participant withdrawals, seven from the trial and five from treatment.

Baseline

Ninety per cent of the participants recruited were female and the mean age was 57 years, with a range of 20–85 years. Mean symptom duration was 8 years, with a range of 5 months to 50 years. Demographics and clinical symptom profiles of the two arms were evenly matched.

Baseline bowel diaries demonstrated a median of 6.0 FIEs per week among PTNS patients, comprising a median of 3.0 urge FIEs and a median of 2.0 passive episodes. Patients in the sham arm experienced a median of 6.9 FIEs per week, with a slightly higher rate of passive FI (median 3.0 episodes) than urge episodes (median 2.5 episodes).

Baseline SMCSs were similar between the arms, with a mean of 14.4 (standard deviation 3.7) in the PTNS arm and 15.4 (standard deviation 4.1) in the sham arm. All 211 participants who completed the SMCS had significant FI, on the basis of their score being > 5 .

Primary outcome

The percentage of patients achieving a $\geq 50\%$ reduction in weekly FIEs was similar in both arms, at 38% in the PTNS arm and 31% in the sham arm [odds ratio 1.283, 95% confidence interval (CI) 0.722 to 2.281; $p = 0.396$].

Secondary outcomes

No significant difference was observed between the PTNS and sham arms in the number of participants achieving $\geq 25\%$, $\geq 75\%$ and 100% reduction in weekly FIEs. There was, however, a significantly greater decrease in total weekly FIEs in the PTNS arm than in the sham arm (difference in means -2.3 , 95% CI -4.2 to -0.3 ; $p = 0.02$). This included a reduction in the number of urge FIEs weekly (-1.5 , 95% CI -2.7 to -0.2 ; $p = 0.02$) but not in the number of passive FIEs (-0.64 , 95% CI -1.67 to 0.40 ; $p = 0.23$).

No significant difference in SMCSs was observed between the two arms following treatment (difference in means -0.047 , 95% CI -1.033 to 0.939 ; $p = 0.93$). No significant differences were seen in the disease-specific (Faecal Incontinence Quality of Life Index and Gastrointestinal Quality of Life Index) or generic (Short Form Questionnaire-36 items) quality-of-life measures between the PTNS and sham arms following treatment.

The improvement in the patient-centred outcomes score was significantly greater in the PTNS arm than in the sham arm (difference in means -0.545 , 95% CI -1.081 to -0.008 ; $p = 0.047$). No significant difference existed in patients' global impression of success between the PTNS and the sham arms (difference in means 0.808 , 95% CI -0.055 to 1.672 ; $p = 0.068$).

There were virtually no differences between the two arms either at baseline or post treatment in respect of either the European Quality of Life-5 Dimensions index or the visual analogue scale, with scores on both scales remaining unchanged over time.

Other outcomes

In the PTNS arm, 57 out of 107 (54%) participants thought that they had received PTNS and 48 out of 107 (46%) participants thought that they had received sham treatment. In the sham arm of the trial, 32 out of 103 (31%) participants thought that they had received PTNS and 71 out of 103 (69%) participants thought that they had received sham treatment. These results are indicative of effective blinding.

Among participants who used loperamide, the majority in both the PTNS arm (33 out of 49; 67%) and the sham arm (32 out of 38; 84%) reported no change in its use throughout the trial. Equal proportions in each arm (4% in PTNS vs. 5% in sham) reported increasing loperamide use. The proportion of patients who were able to reduce their loperamide use was higher in the PTNS arm than in the sham arm (29% vs. 11%); however, this difference was found not to be significant ($p = 0.06$).

Serious adverse events

There were four serious adverse events during the trial; however, none was related to the trial treatment and all were resolved.

Conclusions

The CONFIDeNT (CONtrol of Faecal Incontinence using Distal NeuromodulaTion) study was an adequately powered, well-conducted, definitive trial, carried out to a high standard with an absence of any methodological flaws or serious breaches.

Percutaneous tibial nerve stimulation did not show significant benefit over sham electrical stimulation in the treatment of FI based on the proportions of patients who reported at least a 50% reduction in weekly FIEs. However, among patients who received PTNS, mean total weekly FIEs and mean urge weekly FIEs were significantly reduced, and patient-centered outcomes were significantly improved, compared with patients who received sham treatment.

Based on the evidence presented it would be hard to justify recommending this therapy for the patient population in the trial.

In view of the relatively low costs associated with this treatment and its high acceptability, there may be a justification in continuing to treat a subgroup of patients with troublesome urge FI symptoms in whom directed therapy may cause symptomatic improvement. Further studies of PTNS should be directed at those with urge FI to determine the clinical effectiveness.

Trial registration

This trial is registered as ISRCTN88559475.

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