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Randomized Clinical Trial

Percutaneous tibial nerve stimulation in patients with severe low anterior resection syndrome: randomized clinical trial

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Abstract

Background: Treatment of low anterior resection syndrome (LARS) is challenging. Percutaneous tibial nerve stimulation (PTNS) can improve select bowel disorders. An RCT was conducted to assess the efficacy of PTNS compared with sham stimulation in patients with severe LARS.

Method: This was a multicentre, double-blind RCT. Patients with major LARS score were allocated to receive PTNS or sham therapy (needle placement simulation without nerve stimulation). The study included 16 sessions of 30 min once a week for 12 consecutive weeks, followed by four additional sessions once a fortnight for the following 4 weeks. The primary endpoint was efficacy of PTNS defined by the LARS score 12 months after treatment. Secondary endpoints included faecal incontinence, quality of life (QoL), and sexual function.

Results: Between September 2016 and July 2018, 46 eligible patients were assigned randomly in a 1 : 1 ratio to PTNS or sham therapy. Baseline characteristics were similar. LARS scores were reduced in both groups, but only patients who received PTNS maintained the effect in the long term (mean(s.d.) score 36.4(3.9) at baseline *versus* 30.7(11.5) at 12 months; $P = 0.018$; effect size –5.4, 95 per cent c.i. –9.8 to –1.0), with a mean reduction of 15.7 per cent at 12-month follow-up. The faecal incontinence score was improved after 12 months in the PTNS group (mean(s.d.) score 15.4(5.2) at baseline *versus* 12.5(6.4) at 12 months; $P = 0.018$). No major changes in QoL and sexual function were observed in either group. There was no therapy-associated morbidity. Three patients discontinued the study, but none owing to study-related issues.

Conclusion: PTNS has positive effects in some patients with major LARS, especially in those with faecal incontinence. Registration number: NCT02517853 (http://www.clinicaltrials.gov).

Introduction

Rectal cancer surgery has evolved radically over the past 25 years. Multimodal treatment together with widespread adoption of total mesorectal excision has improved survival[1–3] and increased anal sphincter preservation. This has in turn resulted in a higher incidence of defaecatory disorders that are difficult to manage.

Low anterior resection syndrome (LARS) encompasses bowel dysfunction derived from a rectal resection that ends up in 'toilet dependence', causing detriment to the well-being of the patient[4]. LARS includes faecal incontinence, urgency, stool clustering, and fragmentation. The aetiology of LARS is considered multifactorial. The main causes might be related to direct anal sphincter lesions, damage to the nerves involved in defaecation with anorectal inhibitory reflex annulment, decrease in distensibility and denervation of colonic plasty, and use of preoperative radiotherapy, which can reduce the elasticity of the tissues[4,5]. Currently there is no specific treatment for LARS.

Percutaneous tibial nerve stimulation (PTNS) has been used for faecal incontinence with good success rates[6–8]. The mechanism of PTNS is complex and similar to that described for sacral neuromodulation (SNM). The tibial nerve is a mixed sensory–motor nerve containing L4–S3 fibres that originates from the same spinal segments as the nerves to the pelvic floor. Its stimulation might involve activation of multiple nerve pathways at medullary and brain levels, increasing baseline and stress pressure of the anal sphincters, as well as improving motility and rectal sensitivity[9–11]. The PTNS technique is simple, because the nerve is easily accessed owing to its location at the ankle. It is also an ambulatory, minimally invasive approach and has much lower costs than SNM.

The results of two studies[12,13] have suggested that PTNS may have potential benefits in LARS, but they included a small

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number of patients with short follow-up, and no control group. The aim of the present multicentre randomized study was to assess the efficacy of PTNS compared with sham stimulation in patients with severe LARS by evaluation of changes in bowel disorders, quality of life (QoL), and sexual dysfunction.

Methods

This multicentre, prospective, randomized, double-blind, sham-controlled, parallel-group trial was designed to assess the clinical effect of PTNS in the treatment of patients with LARS. Patients were recruited from two hospitals in Barcelona, Spain: Vall d'Hebrón University Hospital and Bellvitge University Hospital. Colorectal surgeons and rehabilitation therapists from these hospitals participated in the study. The study was registered with ClinicalTrials.gov (NCT02517853).

Eligibility criteria

Inclusion criteria consisted of patients older than 18 and under 75 years, who had undergone anterior resection of the rectum with sphincter preservation for rectal cancer, and who had received definitive surgery at least 1 year previously (rectal resection or ileostomy closure), with major LARS (score over 29). Patients were excluded from the study if they had intestinal segments resected other than rectum, inflammatory bowel diseases, irritable bowel syndrome, metastatic disease at surgery, were pregnant, or had received PTNS previously.

All eligible patients provided written informed consent before undergoing study-related procedures. The study protocol was approved by the Ethical Committee of Vall d'Hebrón and Bellvitge University Hospitals.

Randomization and masking

On enrolment in the study, patients were assigned randomly to one of the two groups in a 1 : 1 ratio to receive PTNS or sham therapy. Randomization was centralized by a computer system using balanced blocks of variable size to ensure equal treatment allocation. Each centre had its own randomization vector. Allocation of patients was concealed from the outcome assessors. The rehabilitation therapist who administered the treatment was the only one who was not blinded. Participants were also blinded to the treatment allocation, and all equipment was hidden from their view.

Procedures

In the experimental group, PTNS was applied according to the Stoller technique[14], using the EV-803P digital transcutaneous electrical nerve stimulation device (Medistim, Plymouth, Minnesota, USA). Briefly, patients were placed in the supine position with the soles of the feet together, and the knees abducted and flexed (frog position). A 34-G stainless steel needle was inserted approximately 4 cm cephalad to the medial malleolus, at a 60° angle between the posterior margin of the tibia and the soleus muscle tendon. A stick-on electrode pad was placed near the arch of the same foot, and the needle was connected to the voltage stimulator. Great toe flexion and patient-reported sensory stimulation in the bottom of the foot were indicators of nerve stimulation. Stimulation was provided at a level of 0.5–10 mA and frequency of 20 Hz with a fixed pulse width of 200 μs, based on patient comfort and responses (toes or foot extension, or tingling sensation under the foot).

In the sham group, a validated sham procedure was used to mimic the feeling of foot stimulation as described previously[15]. Patients lay in the same position as in the PTNS group. A Streitberger needle was used at the tibial nerve insertion site to simulate needle placement. This is a two-piece needle, composed of a handle and blunt-tip shaft that produces a slight prick when it touches the skin; as increased pressure is applied, the shaft of the needle disappears into the handle giving the impression that the needle is actually entering the skin. The needle and surface electrodes were taped in place as in the PTNS procedure. As no electrode needles were inserted, no stimulation was applied to the tibial nerve.

Protocol

All patients in both PTNS and sham groups underwent a total of 16 sessions of 30 min each once a week for 12 consecutive weeks, followed by four additional sessions once a fortnight for the following 4 weeks.

During the initial visit, exclusion and inclusion criteria were checked, including a full medical history record and completion of questionnaires before the start of treatment. After treatment, patients were re-evaluated during a clinical visit after 1, 3, 6, and 12 months by the same investigators, who recorded prospectively all the data on an online case record form specifically created for the study via a web page. The number of PTNS and sham sessions were recorded for each patient to verify treatment compliance.

Outcomes

The primary endpoint was the efficacy of PTNS compared with sham stimulation for the treatment of LARS. A 20 per cent reduction in LARS score was expected 12 months after treatment for patients who underwent PTNS.

The LARS score is an internationally validated, self-administered questionnaire used to assess bowel function after anterior rectal resection[16,17]. It consists of five items: incontinence to flatus, incontinence to liquid stool, frequency, clustering, and urgency. Each item is weighted individually, and a cumulative score is obtained (range 0–42). Bowel dysfunction severity is graded as no LARS (range 0–20), minor LARS (range 21–29) or major LARS (range 30–42).

Secondary endpoints included assessment of faecal incontinence, QoL, and sexual dysfunction. Faecal incontinence was measured using the St Mark's faecal incontinence score, which consists of seven items assessing the type and frequency of incontinence, alteration in lifestyle, need to wear a pad, use of a plug or changes of underwear because of incontinence, use of antidiarrhoeal medications, and ability to defer defaecation for up to 15 min. The total score ranges between 0 (complete continence) and 24 (complete incontinence)[18].

QoL was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30). The QLQ-C30 consists of 30 questions assessing global health status, functional outcome scales (physical, role, emotional, cognitive, and social functioning), and symptom outcome scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea, and financial difficulties)[19]. The scores were generated according to EORTC scoring guidelines. The total score ranges from 0 to 100, and a high scale score represents a higher response level. A high score on a functional scale corresponds to a high or healthy level of functioning, whereas a high score on a symptom scale represents a high level of symptoms. Missing data were handled according to EORTC guidelines[20].

Sexual function was measured by means of validated tools. In men, the International Index of Erectile Function (IIEF-5) was used. This is a five-item questionnaire that evaluates men's sexual functioning, including erectile function, orgasmic function, sexual desire, satisfaction with intercourse, and overall satisfaction. A score of 0–5 is awarded for each of the five questions that examine each main domain. Erectile dysfunction is classified into five categories ranging from none (22–25 points) to severe (5–7 points)[21].

The Female Sexual Function Index (FSFI) was used to measure the six major dimensions of female sexual function (desire, subjective arousal, lubrication, orgasm, satisfaction, and pain) as experienced over the past 4 weeks. The 19 multiple-choice items are answered on a 5- or 6-point scale. Domain scores are calculated by summing the responses for the items in each domain, then scaling this total with a multiplier that constrains all domains to the same range. A total score for the measure can be obtained by summing the individual domain scores. The minimum score is 2 points and maximum score is 36 points. A score below 26.55 is classified as sexual dysfunction[22].

Statistical analysis

According to data from patients with LARS treated at the authors' hospitals, the subgroup of patients with severe LARS had a mean LARS score of 35.6. Assuming a standard deviation of 7.9 points, a total of 42 patients (21 patients per group) were required to detect a difference of at least 7 points (20 per cent decrease) between the two treatment groups, with 80 per cent power and two-tailed $\alpha = 0.05$, and anticipating a 15 per cent drop-out rate.

Descriptive summary statistics for continuous/quantitative variables are provided as mean(s.d.) for normally distributed data. For the primary and secondary endpoints, changes in follow-up from baseline were reported using the effect size with 95 per cent confidence intervals.

Differences between groups were assessed using parametric or non-parametric tests, as appropriate. To evaluate the effectiveness of the intervention with PTNS (primary endpoint), LARS scores in the two groups were compared using the Student *t* test if the distribution was normal or the Mann-Whitney *U* test if the distribution was skewed. Secondary endpoints (effects on faecal incontinence, QoL, and sexual functioning) were tested for statistical significance using paired-samples *t* tests for normally distributed variables and Wilcoxon signed-rank tests for non-normally distributed variables. Differences between groups were tested with independent-samples *t* tests for normally distributed variables and Mann–Whitney tests for those with a non-normal distribution. All analyses were undertaken according to the intention-to-treat (ITT) principle. $P < 0.050$ was considered to indicate statistical significance. Analyses were performed using SAS System® for Windows® version 9.3 (SAS Institute, Cary, North Carolina, USA).

Results

Between September 2016 and July 2018, a total of 46 eligible patients (of 48 screened) were assigned randomly to two groups (23 per group) (*Fig. 1*). The trial was stopped after reaching the number of patients required. The first group received PTNS and the second sham stimulation. A total of three patients discontinued the study, but none for study-related issues: one patient in the sham group developed peritonitis from a late leak of the colorectal anastomosis; in the PTNS group, one patient underwent cardiac pacemaker implantation and the other had distant recurrence. Ten patients were lost to follow-up (2 in PTNS group and 8 in sham group). No deaths were reported during follow-up.

Demographic and other baseline characteristics

The mean(s.d.) age for the whole study population was 62.2(7.2) (range 48–75) years, and 27 of the 46 patients were men. Patient demographic and baseline characteristics are summarized in *Table 1*. Eighteen patients in the control group and 19 in the PTNS group completed all 16 PTNS sessions.

Primary endpoint: changes in low anterior resection syndrome score

LARS scores improved in all participants in both groups from baseline to 1 month. In the sham group, the mean(s.d.) LARS score fell from 36.3(3.2) at baseline to 32.8(7.7) at 1 month ($P = 0.042$). In the PTNS group, the mean LARS score fell from 36.4(3.9) at baseline to 29.7(13.0) at 1 month ($P = 0.014$). LARS scores at 12 months after treatment remained lower than baseline values in the PTNS group (30.7(11.5); $P = 0.018$), but not in the sham-treated patients (33.9(6.6); $P = 0.209$). The effect sizes at 12-month follow-up were –2.2 (95 per cent c.i. –5.8 to 1.4) and –5.4 (–9.8 to –1.0) in the sham and PTNS groups respectively. In the PTNS group, the mean reduction in LARS score compared with baseline was 18.4 per cent at 1 month and 15.7 per cent at 12 months ($P = 0.014$ and $P = 0.018$ respectively), whereas the LARS score decreased by 9.6 per cent at 1 month and 6.6 per cent at 12 months in the sham group. However, there were no statistical differences between the groups at the same follow-up times (*Table 2* and *Fig. 2*).

Secondary endpoints

Changes in faecal incontinence

From baseline to 1 month, patients in the sham and PTNS groups showed a mean reduction of 1.5 points ($P = 0.023$) and 4.2 points ($P < 0.001$) in St Mark's faecal incontinence score respectively. At 12 months, the effect on incontinence was no longer observed in the sham therapy group (increase of 0.3 points; $P = 0.706$), whereas the decrease in the continence score was maintained in the PTNS group (3 points; $P = 0.018$) (*Table 3* and *Fig. 2*).

Changes in quality of life

One month after intervention, QoL measured by the EORTC QLQ-C30 had improved in role and emotional functioning domains only in patients who received PTNS. This improvement was not maintained at 12 months. There were no changes for other domains and symptoms in the PTNS and sham groups at any time of assessment (*Table S1* and *Fig. 3*).

Changes in male sexual function

IIEF-5 scores did not change during follow-up. There were no differences between groups in changes in mean IIEF scores between baseline and 12-month follow-up (sham: mean(s.d.) 10.7(6.1) *versus* 11.3(6.2), $P = 0.644$; PTNS: 9.5(5.9) *versus* 9.0(6.1), $P = 0.847$) (*Table S2* and *Fig. S1*).

Change in Female Sexual Function Index

At baseline, the mean FSFI score was higher in the PTNS group than in the sham group (mean(s.d.) 23.4(6.0) *versus* 13.6(10.0); $P = 0.032$). Similarly, at 12 months after treatment, patients in the PTNS group had a higher mean FSFI score than those in the sham group (19.4(9.2) *versus* 5.9(6.2); $P = 0.009$). The mean change from baseline was similar in the two groups (*Table S3*and *Fig. S1*).

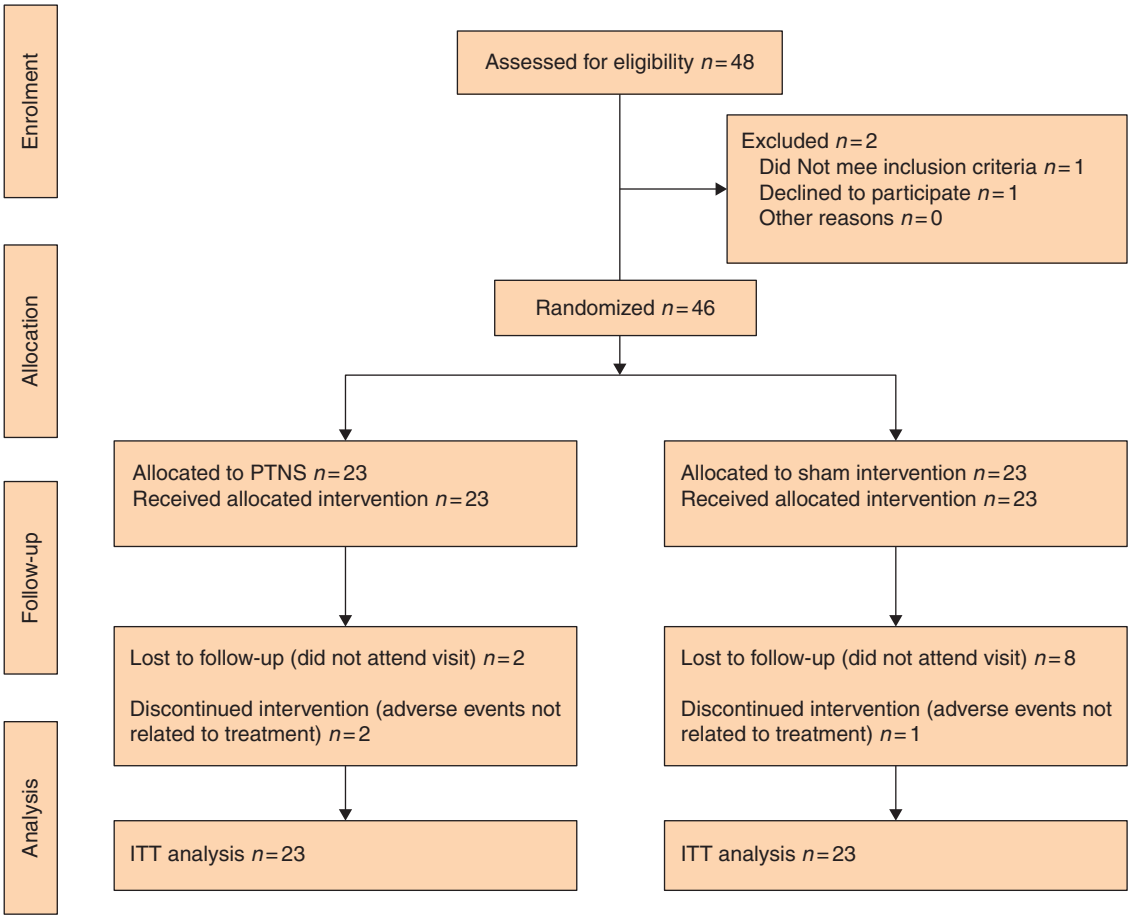

Fig. 1 CONSORT diagram for the trial

PTNS, percutaneous tibial nerve stimulation; ITT, intention to treat

Table 1 Baseline demographic and clinical characteristics

	Sham (*n* = 23)	PTNS (*n* = 23)
Age (years)*	61.7(7.2)	62.7(7.2)
Sex ratio (M : F)	11 : 12	16 : 7
BMI (kg/m^2)*	27.0(6.3)	27.6(2.9)
Extent of mesorectal resection		
Total	19	21
Partial	4	2
Temporary stoma		
No	4	6
Yes	19	17
Anastomotic dehiscence		
No	23	22
Yes	0	1
Preoperative chemotherapy		
No	4	4
Yes	19	19
Postoperative chemotherapy		
No	2	3
Yes	21	20
Preoperative radiotherapy		
No	4	2
Yes	19	21
Short course	2	0
Long course	17	21
Postoperative radiotherapy		
No	22	22
Yes	1	1
Short course	0	0
Long course	1	1

*Values are mean(s.d.). PTNS, percutaneous tibial nerve stimulation.

Table 2 Within- and between-group changes in low anterior resection syndrome score between baseline, and 1- and 12-month follow-up

	Sham		PTNS		P†
	n	Score	*n*	Score	
Baseline	23	36.3(3.2)	23	36.4(3.9)	0.902
1 month	15	32.8(7.7)	20	29.7(13.0)	0.411
Change from baseline*		–4.1(–8, –0.2)		–6.8 (–12.0 –1.5)	
P (baseline *versus* 1 month)‡		0.042		0.014	
3 months	16	34.4(5.5)	20	29.5(9.9)	0.081
6 months	13	34.9(4.6)	18	29.4(13.7)	0.174
12 months	14	33.9(6.6)	19	30.7(11.5)	0.370
Change from baseline*		–2.2 (–5.8, 1.4)		–5.4 (–9.8, –1.0)	
P (baseline *versus* 12 months)‡		0.209		0.018	

Values are mean(s.d.) unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. PTNS, percutaneous tibial nerve stimulation. †Independent-samples *t* test; ‡paired-samples *t* test.

Discussion

PTNS did not result in a significant treatment response compared with sham stimulation in patients with LARS based on the primary endpoint. However, the LARS score did decrease by 15.7 per cent by 12 months after treatment in patients who received PTNS.

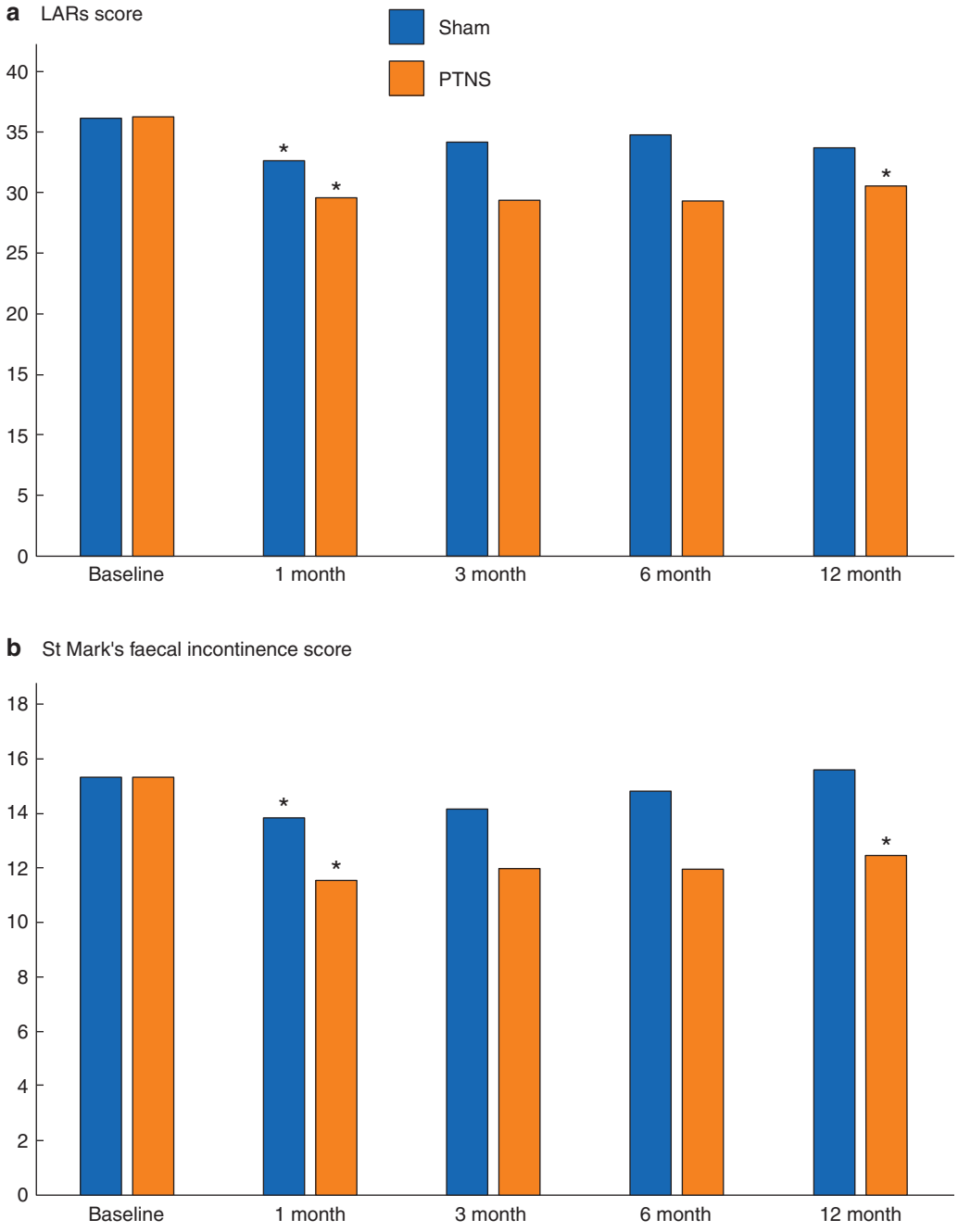

Fig. 2 Mean low anterior resection syndrome scores and St Mark's faecal incontinence scores in sham and percutaneous tibial nerve stimulation groups over time

a Low anterior resection syndrome (LARS) scores and **b** St Mark's faecal incontinence scores. PTNS, percutaneous tibial nerve stimulation. *$P < 0.050$ *versus* baseline in same group (paired-samples *t* test).

Two previous prospective, non-controlled pilot studies assessed the efficacy of PTNS for LARS. The first[12] reported on 21 patients with major and minor LARS who underwent 12 sessions of PTNS for 8 weeks. At 6-month follow-up, the mean LARS score had decreased from 32 to 27 points after PTNS ($P = 0.009$). Vigorita and colleagues[13] performed PTNS in two phases in 10 patients with major and minor LARS. In the first phase, all patients received PTNS twice a week for 6 weeks (12 sessions); stimulation was continued into a second phase with one session per week for patients who improved after the first one. The authors reported that seven patients responded positively after the first phase. Of these, three patients were downgraded from major to minor LARS, two from minor to no LARS, and two patients did not show improvement in LARS score after the second phase; however, the patients reported better outcomes after treatment when clinical assessment was done by evaluation of defaecatory diaries.

Patients treated with PTNS in the present study also showed a decrease in LARS score, but this might not have reflected the actual overall clinical improvement experienced. The sensitivity of this score has proved worrisome with respect to measurement of outcomes after any therapeutic approach for LARS. Clustering and urgency are assigned a score of 9 and 11 points respectively if they occur at least once a week. During assessment after

Table 3 Within- and between-group changes in St Mark's faecal incontinence score between baseline, and 1- and 12-month follow-up

	Sham		PTNS		P†
	n	Score	*n*	Score	
Baseline	23	15.4(5.3)	23	15.4(5.2)	0.978
1 month	16	13.9(6.2)	20	11.6(5.8)	0.264
Change from baseline*		−3.4 (−6.2, −0.5)		−4.2 (−6.3, −2.1)	
P (baseline *versus* 1 month)‡		0.023		< 0.001	
3 months	16	14.2(5.3)	20	12(6.9)	0.318
6 months	16	14.9(5.4)	18	12(6.9)	0.223
12 months	14	15.7(5.9)	19	12.5(6.4)	0.145
Change from baseline*		−0.6 (−4.2, 3)		−3.0 (−5.4, −0.6)	
P (baseline *versus* 12 months)‡		0.706		0.018	

Values are mean(s.d.) unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals. PTNS, percutaneous tibial nerve stimulation. †Independent-samples *t* test; ‡paired-samples *t* test.

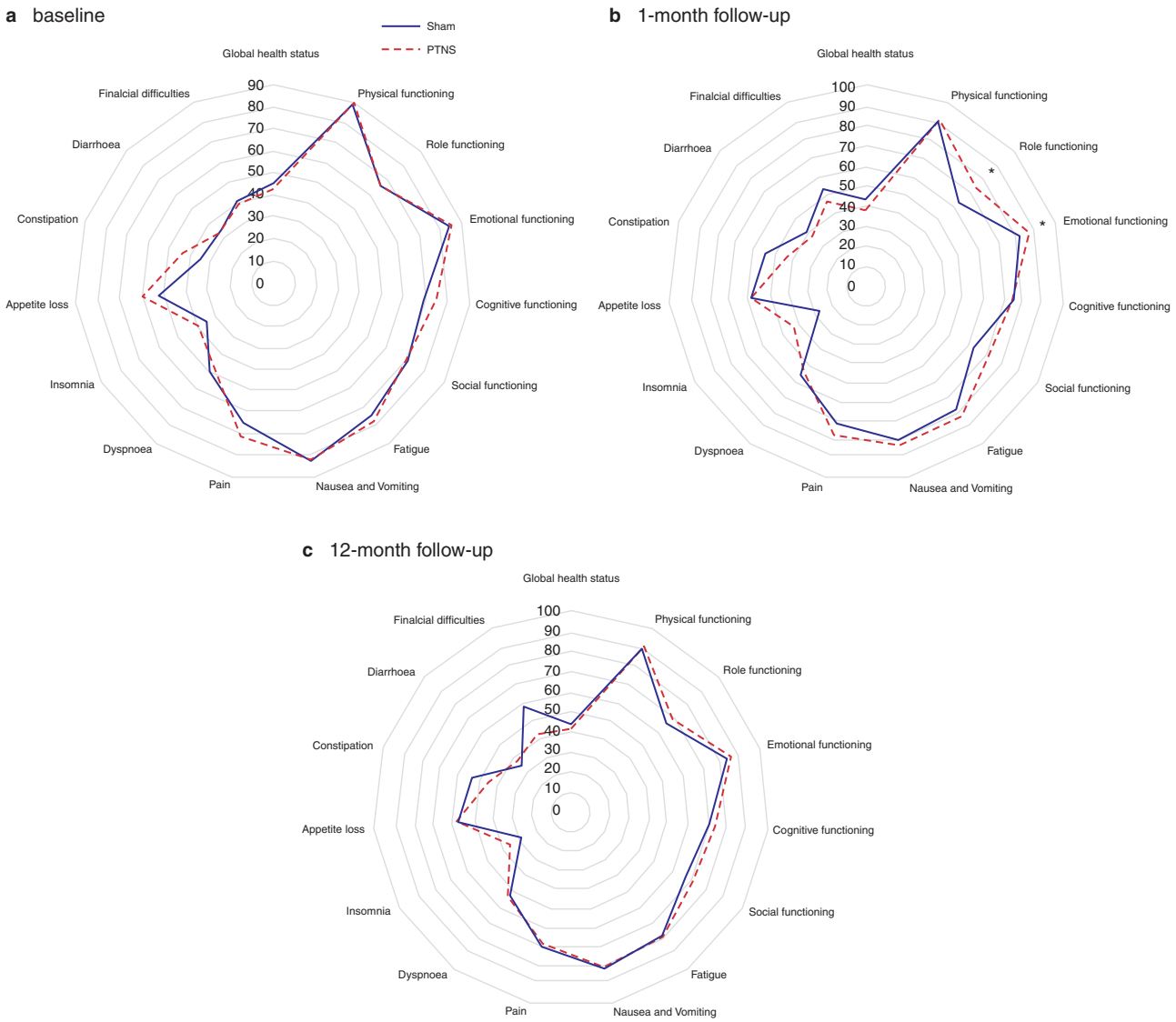

Fig. 3 EORTC QLQ-C30 quality-of-life scores at baseline, and 1- and 12-month follow-up in sham and percutaneous tibial nerve stimulation groups
PTNS, percutaneous tibial nerve stimulation. *$P < 0.050$ *versus* sham. (paired-samples *t* test).

treatment, it was found that many patients did experience a reduction in the total number of episodes of clustering and urgency, but this did not translate into the LARS score as they reported at least one episode of such symptoms per week. Some patients also reported that they found it difficult to choose between the options available.

This study also aimed to analyse the effects of PTNS *versus* sham therapy on faecal continence as measured by the St Mark's

faecal incontinence score. This score improved in both groups by 1 month after treatment. At 12-month follow-up, the reduction was sustained only in the PTNS group, but without superiority over sham therapy. Contradictory results have been reported regarding the efficacy of PTNS for faecal incontinence. Although one RCT[23] reported short-term benefits, two others[24,25] failed to demonstrate any benefit of PTNS compared with sham therapy. Rectal cancer treatments lead to changes in function and anatomy that can result in LARS via a multifactorial aetiological model, in which surgery but also radiotherapy play a central role. The reduced tissue elasticity and nerve damage after radiotherapy and surgery could explain the finding of minor or no changes after PTNS in LARS compared with idiopathic faecal incontinence[4,5].

The partial improvement observed in the sham group is difficult to explain. It has been reported that sham therapies can also benefit organ function and patients' overall health through positive expectations and behavioural conditioning processes that can even persist over time[26,27]. Furthermore, the Streitberger needle used in this study has been shown to activate the dorsolateral prefrontal cortex, which is associated with a placebo effect[28]. Being the first trial to included sham therapy for LARS, the authors assume that these factors could have explained the positive changes noted in the sham control group.

No significant changes were noted in QoL in any group, except for role and emotional functioning at 1 month after PTNS. This could translate into less limitation to work and resumption of other activities in patients with LARS. The global health status at baseline in both groups was lower than the score for the reference population, which comprised all cancer stages of colorectal cancer and was published by the EORTC (44 in average for the population in this study *versus* 60.7 in the reference population)[29].

PTNS could also play a role in the treatment of sexual dysfunction, although surgical nerve damage during rectal cancer surgery, even with careful nerve preservation techniques, might preclude the potential effects of this therapy. In the present study, men and women in both groups presented with sexual dysfunction at baseline according to the IIEF-5 and FSFI questionnaires. In men, no significant differences were observed either between or with groups over time. In women, a decrease in FSFI scores was noted at 1-year follow-up especially in the sham group. The decrease was smaller in the PTNS group, which might be explained by some effects of the therapy. Similar outcomes regarding sexual dysfunctions in LARS were found in another study after treatment for PTNS[12].

This study has limitations. The exclusive use of tests to determine endpoints and to assess the evolution of LARS after treatment could have left positive clinical outcomes undetected. Nowadays, owing to the complexity of LARS, thorough clinical evaluation and assessment of bowel diaries combined with multiple validated tests should be the adequate evaluation. No assessment was made of urinary disorders, which are also common in patients who undergo rectal resection. The PTNS protocol of 12 sessions was the same as that applied to non-LARS-related disorders. Because of the surgical changes, it is possible that patients with LARS needed a more intense protocol or more sessions to achieve clinical improvement. Finally, the drop-out rate was relevant, and might have affected the results. However, the analysis provides a real-life insight, avoiding exaggerated, unrealistic treatment effects. Inclusion criteria were strict and follow-up included specific QoL and sexual dysfunction assessment.

PTNS could have positive effects in some patients with major LARS, but its clinical significance might be limited. This inexpensive therapy could be acknowledged and included in multimodal pelvic floor rehabilitation before escalation to invasive techniques, especially in patients with incontinence. However, adequate discussion with patients should take place before deciding on this treatment, so that realistic expectations can be ensured.

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Supplementary material

Supplementary material is available at *BJS* online.

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