A prospective trial of temporary sacral nerve stimulation for constipation associated with neurological disease.

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Conflicts of Interest

ABSTRACT

Aim: The study assessed the effectiveness of temporary sacral nerve stimulation (SNS) in patients with constipation associated with neurological disease using an off-on-off design and evaluated the long-term response in patients undergoing permanent SNS.

Method: Patients with chronic constipation associated with neurological disease receiving specialist clinic care at the University Hospital North Durham over a two-year period, were recruited to a trial of SNS. Recordings of bowel function were made for 6 weeks (baseline) and a temporary electrode was then inserted and recordings were made for the next three weeks (stimulation). The electrodes were then removed and assessment was continued for a further three weeks (post-treatment). Patient-assessed questionnaires were used to determine the global assessment of the severity of constipation (GA), symptoms (PAC-SYM) and quality-of-life (PAC-QOL, EuroQOL EQ-5D-3L and EQ-VAS). Information was obtained on bowel function and medication. Physiological data of transit and laser Doppler flow cytometry to measure mucosal blood folw were also available.

Results: Twenty two patients were recruited of whom 18 patients completed the trial. GA constipation reduced significantly during temporary SNS from -1.09, 95% confidence interval [CI]-1.59 to -0.59 (p=0.0003). PAC-SYM and PAC-QOL showed similar improvements. There was also a significant fall in the time spent in the toilet (p=0.04) and a decrease in laxative use (p=0.03). Twelve (67%) patients responded to temporary SNS and received a permanent implant with long-term success in 50%.

Conclusions: SNS can be effective in treating some patients with refractory severe neuroconstipation. A response to temporary SNS may predict long-term benefit in only half the patients undergoing permanent SNS.

What does this paper add to the literature?

The paper presents a study of SNS in a subset of patients with constipation associated with neurological disease. A prospective trial in this group of patients has not previously been reported in the literature. This study has helped the investigators to design a future SNS study focusing on the identification of patients most likely to gain long-term benefit.

INTRODUCTION

The most common neurological diseases associated swith constipation are multiple sclerosis and spinal injury, with constipation being present in about half of such patients[1-3]. About 95% of patients with spinal injury require some form of treatment for constipation and more than half have psychological distress caused by their symptoms[3]. Constipation associated with neurological disease is difficult to treat because of the many pathophysiological mechanisms involved. In spinal cord disease or injury, the distal colon is the most affected. In lesions above spinal cord segment L2 (supraconal), sympathetic inhibition is lost. The pattern of injury is similar to an upper motor neurone lesion and causes hyper-reflexia and hypertonia of the rectum [4]. Whole gut transit is

slowed and can lead to reflex defaecation and incontinence. In cauda equina lesions, there is a lower motor neurone-type presentation as the sacral reflex arc is disturbed causing hypotonia and hyporeflexia[5]. Both suparconal and conal injuries lead to faecal loading and impaction. This results in severe constipation leading to faecal soiling. The most severe dysfunction is seen in complete spinal cord injury (SCI). In multiple sclerosis (MS), the pathophysiology is similar but the lesions occur at many levels resulting in variable presentations. Previous studies have described colonic dysfunction in patients with severe MS [6] and patients with SCI[7, 8] secondary to visceral neuropathy causing severe constipation. In addition, many patients have reduced mobility adversely affecting bowel function and promoting severe constipation and faecal impaction [9]. Long-term medication with anticholinergics used for bladder dysfunction or opioid analgesics disturbs an already poor bowel function.

Management is difficult in this heterogeneous group of patients with multiple aetiologies. The goal of therapy is to provide effective symptom relief while maintaining patient dignity and independence. The options for managing neuroconstipation include manual evacuation with digital stimulation, abdominal massage, laxatives, suppositories and/or enemas and interventional measures including retrograde rectal irrigation or faecal diversion by stoma formation. The aim of laxative therapy is to achieve a stool consistency that will allow easy passage avoid faecal soiling between defaection. Patients with incomplete SCI having some control over bowel function seem to benefit from laxative therapy [4, 10]. This may not be achievable in other patients and can result in significant unplanned evacuations or seepage between visits to the lavatory. Transanal irrigation is a safe and effective treatment but has to be performed frequently and requires long periods in the toilet [11]. The evidence for transanal irrigation in patients with MS is limited to observational studies with mixed reports. Surgery for diversion carries a significant risk of early or late complications[12].

Sacral nerve stimulation is effective in many patients with faecal incontinence who have failed conservative management[13]. Temporary SNS provides a diagnostic and screening stage and helps to identify patients who may benefit from permanent implantation. The National Institute for Clinical Excellence has approved it for faecal incontinence [14], but there is less clinical information in constipation. There is some experience of its use for slow tranasit constipation [15], but no study has to date prospectively evaluated it for constipation associated with neurological disease.

There is evidence that patients with incontinence due to a neurological cause had the best outcome[16]. Consequently, the aim of this study was to investigate the possible effectiveness of temporary SNS in patients with neuroconstipatino and to evaluate the long term response in patients undergoing permanent SNS implantation.

METHOD

Design

An off-on-off trial design was used to evaluate temporary SNS prospecively in 20 patients with constipation associated with spinal cord injury or disemninated sclerosis . Pre-treatment severity and stability of constipation was assessed for six weeks (baseline) before insertion of a temporary sacral nerve electrode inserted bilaterally under a general anaesthetic to minimise the risk of displacement and laterality bias. Patients were then assessed for three (stimulation) at which point the electrodes were removed and the patients assessed for three more weeks (post-treatment).

Stimulation thresholds were recorded on insertion of the electrodes (beginning of week 7) and at the removal (end of week 9), using a temporary pulse generator delivering a maximum of 10 volts. The correct positioning of electrodes was confirmed by observable anal sphincter contraction and great toe plantar flexion. Patients with a successful trial of bilateral SNS (see criteria below) received a permanent implanted pulse generator with bilateral barbed (tined) leads under general anaesthetic. Criteria for permanent implantation after temporary electrode insertion included an

improvement of 2.0 on the GA scale for constipation and an improvement of the PAC-SYM score by 0.5 from baseline. The medium-term success rate of permanent implantation was determined by a patient reported outcome for global satisfaction and consistent symptom scores with minimal regression to pre-treatment baseline.

Patients

Patients with neurological disorders were recruited between December 2007 and December 2009 at a tertiary, specialist constipation clinic in the University Hospital North Durham. All had severe constipation, refractory to treatment with changes of diet, laxatives, suppositories, enemas and rectal irrigation. Patients had previously undergone standard clinic assessment including a history, physical examination including rectal examination, blood investigation, symptom and quality of Life assessment, intestinal transit estimation and flexible sigmoidoscopy.

Patients gave informed consent following an initial discussion followed by verbal and written explanation of the study. They were free to withdraw from the study at any point. Data were retained to the point of withdrawal. Carers and primary care physicians were informed of the patient's decision to participate. The study had ethical approval (LREC number: 07/H0903/45) and was registered with UK Clinical Research Network Study Portfolio (Study ID: 4594).

Inclusion/exclusion criteria

Inclusion criteria were 16 years or older, neurological disorder (MS or spinal disease), ROME-III constipation criteria fulfilled, multiple sclerosis or spinal cord injury of at least 6-months duration, spending 30 minutes or more attempting defaecation at least every other day, abdominal discomfort before or during defaecation and symptoms not adequately relieved by standard treatment.

Patients were excluded if they had any of the following features: unfitness for general anaesthetic, severe psychiatric disease, persistent diarrhoea not due ton laxatives, decompensated cardiac, respiratory, endocrine, renal, or hepatic disease, progression of neurological disease within the

previous 12 months, active systemic infection, pregnancy or trying to become pregnant and mental inability to give informed consent.

End point

The primary endpoint was a weekly, patient-assessment (GA) of constipation symptoms using a five-point Likert scale, score 1 (none) to 5 (very severe). Secondary outcome measures included a weekly assessment of faecal incontinence, symptoms (PAC-SYM),disease specific quality of life (PAC-QOL); and health status (EuroQOL, EQ-5D and EQ-VAS). The Patient Assessment of Constipation (PAC) measure consists of two validated scales, PAC-SYM (a 12-item measure of symptom severity with three symptom sub-domains, (abdominal, rectal and stool) and PAC-QOL (a 28-item disease-specific measure of health-related Quality of life with four subdomains (physical, psychosocial, worries and concerns and satisfaction) [17, 18]. For both measures, individual items, sub-domains and aggregated scores were scored 0 (none) to 4 (very severe). EuroQOL measures were repeated before, during and after temporary SNS at three-week intervals. EuroQOL is a standardized instrument with two components providing a generic valuation of health-related quality of life that has been widely used[19]. EQ-5D-3L is a dimensional representation of health-related quality of life including mobility, self-care, usual activities, pain/discomfort, anxiety/depression, each scored at one of three levels. The response is converted to a health preference score ranging from 0 (death) to 1 (perfect health). EQ-VAS is a 20cm vertical visual analogue scale, scoring 0 (worst state of health) to 100 (best state of health). EuroQOL has been evaluated in IBS and IBD [20, 21].

Patients completed a daily diary from week four to nine (three weeks of baseline, during stimuation, including daily stool frequency, time spent in the toilet, episodes and type of faecal incontinence, manual evacuation, laxative intake and laxative score. Laxative intake was documented as more, same or less than average use. Objective measures included a study of transit time and laser Doppler flowcytometry (LDFC) measurement of rectal mucosal blood flow, at baseline and during stimulation (at 3 and 9 weeks). LDFC provides a validated quantitative measure of extrinsic autonomic nerve

activity of the GI tract. Laser Doppler measurements of rectal mucosa have shown improvement in blood flow after SNS suggesting a potentially positive autonomic neuromodulatory role for SNS [23]. LDFC was conducted during flexible sigmoidoscopy with the patient in the left lateral position, averaging four sites in the rectum 10cm from the anal verge, 90 degrees apart [22, 23]. Longer term follow-up of patients receiving permanent implant included assessment of GA constipation, PAC-SYM and PAC-QOL scores. Adverse events arising during the study were assessed for severity, nature and outcome, being monitored by a trial steering group.

Follow-up

For each participant the total duration of the temporary SNS protocol was twelve weeks, from when consent was confirmed. Patients receiving permanent SNS were subsequently followed-up routinely in a specialist outpatient clinic.

Statistical analysis

Baseline scores were averaged for the first six weeks. Scores from weeks 8 and 9 were used for the stimulation phase and week 12 scores were used for the post-treatment phase. Weeks 7, 10 and 11 were excluded from the analysis to allow stabilisation following the stimulation phase. Baseline, stimulation and post-treatment scores were compared using the paired Student's t-test. The validity of parametric testing was explored using the Kolmogorov–Smirnov test to compare the distribution of test variables against a theoretical normal and Wilcoxon's signed-rank test was used to compare non-parametric variables. The Mann Whitney U test was used to compare the scores of responders and non-responders.

The study was originally designed with a sample size of 30, having 94% powerusing as paired t-test with 0.05 two sided signifance to detect a difference in the means of 2.0 in a global symptom assessment 10 point scale assuming a standard deviation of 3.0.. A five-point scale was substituted meaning that the change became 1 point with standard deviation 1.5. Eighteen patients completed

the temporary phase providing *post-hoc* power of 76% in the evaluated cohort.

RESULTS

Twenty-two patients were recruited of mean age of 52 (38-69) years including 14 (64%) females. Fourteen (64%) had multiple sclerosis, 5 (23%) spinal cord injury (cauda equina lesion 2, incomplete lumbar spine injury 1, complete thoracic spine injury 1 and incomplete cervical spine injury 1), 1 autonomic dystonia, 1 spinal myoclonus and 1 had a history of myleitis secondary to polio. Eight patients had normal mobility, in six it was reduced and eight were wheelchair-bound. Four patients dropped out between recruitment and implantation, two deciding to continue with conservative treatment and two experiencing unexpected comorbidity. Eighteen patients started the temporary phase and 16 provided complete score data over the 12 weeks.

Primary end point

The global assessment of constipation (GA) scores from weeks 1 to 12 showed a clear pattern of improvement (Figure 1). The change seen between the baseline and the stimulation period (weeks 8 and 9) was -1.09, 95%CI -1.59 to -0.59 [p = 0.0003]. At the end of the post-treatment period this had reduced to -0.16, 95%CI -0.54 to - 0.23 [p=0.40] (Table 1).

Secondary end points

Faecal continence and patient assessment of symptoms (PAC-SYM) score

Faecal incontinence symptom levels were low at baseline and varied little during the study, consistent with prior expectation. The PAC-SYM score improved during the stimulation phase by -0.73, 95%CI -1.06 to -0.39 [p=0.0003] and had not quite returned to the pre-intervention level at the end of the post-treatment phase (-0.29, 95%CI: -0.58 to -0.01 [p=0.04]. Over the 12-week period sub-domain scores qualitatively

reflected the pattern found in the overall PAC-SYM score (Table 1).

Patient Assessment of Constipation (PAC-QOL)

The PAC-QOL score improved during the stimulation phase (-0.68, 95%CI -1.02 to -0.33, p=0.0008 and was similar to the baseline level at the end of the post-treatment phase, with a change of -0.10, 95%CI -0.35 to 0.16 [p=0.44].   As with PAC-SYM, sub-domain scores qualitatively reflected the pattern found in the overall PAC-QOL score (Table 1).

Euro QOL Health Questionnaire (EQ-5D-3L and EQ-VAS)

There was a suggestion that the EQ-5D-3L score improved during the stimulation phase although this was not statistically significant (0.10, 95%Cl -0.04 to 0.24 [p=0.16]. The EQ-5D-3L score at the end of the post-treatment phase was similar to the baseline phase with a change of 0.03, 95%CI -0.12 to 0.18 [p=0.68]. The poor EQ-5D scores were poor in this patient group, and they were similar in all three phases (Table 1).

Daily Diary

There were non-significant reductions in the frequency of defaecation (-0.25/week, 95%CI -0.68 to 0.18 [p=0.23] and the frequency of episodes of faecal incontinence (-0.86, 95% CI -2.11 to -0.39 [p=0.016]) with episodes reduced to zero during stimulation. There were significant reductions in time spent) in the toilet (-6.5m, 95%CI -12.8 to -0.3 [p=0.04] and a reduction in laxative use (-0.10, 95% CI -0.28 to -0.01 [p=0.03] (Table 1). There was no significant change in the transit time during stimulation compared with baseline (3.9 hours 95% CI -1.0 to 8.8 [p=0.11]. LDFC scores were similar before and during treatment (Table 1). The global assessment of constipation was strongly correlated with PAC-QOL (r=0.898, p<0.001) but was not significantly correlated with PAC-SYM (r=0.357, p=0.17)

Long-term Data

In the twelve responders who received an implantable pulse generator the mean length of time to follow-up was 19.9 +/-7.5 months. Long-term success determined by clinical assessment occurred in six patients (50%, 95%CI 21% -79%). Numbers were too small to explore possible factors related to long-term response, although MS patients group appeared to do better than other patients (response rate 63% vs. 25%) although this difference was not statistically significant [p=0.30].

Adverse events

There was no case of bleeding or infection. No fracture of the wire electrodes was reported, but one wire displacement occurred. This was repositioned in the outpatient clinic without any subsequent need for resiting. There were a few incidents in which patients reported a decrease in the effect of SNS during an exacerbation of MS. This was rectified in most cases by reprogramming the stimulator settings. Patients who did not improve after reprogramming experienced failure owing to a significant diminution in effect.

DISCUSSION

In this prospective trial of temporary SNS in 20 patients with constipation associated with neurological disease, patient-assessed global assessment of constipation (GA-constipation), PAC-SYM and PAC-QOL scores improved significantly during temporary stimulation with diminishing benefit after cessation. There was no pattern of change in faecal incontinence. The EuroQoL assessment were included to provide estimates of variance to help design future studies but were not anticipated to demonstrate change in this trial.

Our findings support the hypothesis that SNS may modulate spinal pathways[28] and vagal afferents leading to cortical activation[29]. Patients with MS may have unstable disease and this can make

assessment of therapy difficult. To minimise bias from disease progression, only MS patients with stable disease and no exacerbations in the preceding 12 month period were recruited. EQ-5D was utilized as a generic objective measure to observe change in mobility, self-care and daily activities. None of the trial patients reported disease progression on follow-up visits and there was no deterioration in EQ-5D scores.

The quality of life of these patients with neurological disease was very poor as demonstrated by the baseline scores and constipation exacerbated the degree of suffering. Patients reported to having a time-consuming, daily bowel regime and most had difficulties with mobility, dignity and independence. Patients with neurogeenic constipation experience a high number of failed and incomplete attempts at evacuiation. SNS may have helped this symptom as would be reflected by fewer defaecations, but the stgudy did not record the completeness of evacuation. This would however be related to the time spent in the toilet and the reduced use of laxatives. Some of the patients commented on an improvement of bowel function during the stimulation phase.

Transit was moderately delayed during baseline assessment and in contrast to a previous study [15] it did not improve during stimulation. This may be due to underpowering of the study. Plain abdominal X-rays to identify ingested shapes rather that real-time scintigraphy may be inadequate to capture the irregular progress of stool through the bowel[24]. Another report on the effect of SNS on gastrointestinal motor function in patients with neurogenic constipation showed no change in gastric emptying, small intestinal or colonic transit[25]. It is therefore more likely that the improvement produced by SNS in some patients in the present study was due to improved rectal emptying rather than improved transit, in keeping with fewer but more complete evacuations

LDFC measurements did not show increasing mucosal circulation with increasing stimulation voltage, as might have been anticipated[26]. Lack of apparent change may be due to lack of effect of SNS on

autonomic efferent function, pathophysiological differences, voltage threshold effects, or lack of power of the study.

A low stimulation threshold to induce improvement has been reported to predict a better long-term result , in faecal incontinence [27] but our findings did not confirm this for neurogenic constipation. All the patients were able to feel an impulse on each side during the stimulation phase, but despite this and in the absence of any evidence to suggest that bilateral stimulation is better, we felt that bilateral insertion of the electrodes would give the patient the optimal chance of havinf a response.

Six of 12 patients receiving permanent SNS reported a satisfactory long-term response. Analysis of possible factors that might have been related to a response was not possible owing to the small number of patients alsthough those with MS may have derived more value than those with SCI.
If so it may be that this is explained by the continued pre3sence of still functioning ascending spinal pathways in MS.
Further research is needed to refine the estimation of effectiveness and identify which patients may benefit most. The NHS tariff for permanent SNS is typically around £15,000 and use in neurogenic constipation does not generate the cost savings that occur when used in faecal incontinence. For it to become economically acceptable a more effective method of identifying long-term responders is required.

The global assessment of constipation, PAC-SYM and PAC-QOL have been robustly developed and validated [17, 18, 30], but test-retest assessment is the one area where they have not been well studied. Although the number of participants in this study was small, the results of these measures over six weekly pre-treatment assessments were remarkably stable lending further support to their use as measures of outcome.

Limitations of the study

The design of the study was not able to differentiate between a response due to active stimulation and the broader question whether this would be indicative of the subsequent susses of treatment in the event of permanent implantation. Thus it could not exclude a placebo response, which would by definition be transient. The possibility of a placebo response could have been explored using a controlled trial design including sham stimulation either in the same patient or between patients. This was not followed becauise initial consultation with patients at the design stage indicated that they would not want to participate in a study which contained the possibility of no active treatment. A sham stimulation would furthermore be difficult to control technically. Additionally the off-on-off design permitted assessment of the time taken for symptoms to change in relation to the changes in stimulation, which would be useful information for any future study We hoped that the inclusion of objective physiological measures such as transit time and mucosal blood flow estimation would provide an additional level of evidence that any response was due to the treatment rather than placebo. In the event this was not the case since neither changed pduring the stimulation phase.

Despite the intention to recruit 30 patients according to the power calculation, recruitment declined during the second year of the study and in the end only 20 patients were studied. Hence, the study was under-subscribed during the two-year recruitment window.

Recent studies of constipation have used a spontaneous complete bowel movement (SCBM) as a primary outcome measure [31, 32]. This is probably more informative than a simple measure of bowel frequency since it distinguishes normality from stool clustering and the dissatisfaction of incomplete emptying. This may be particularly important in neurogenic constipation and we would recommend the use of SCBM as an outcome measure in future studies.

Temporary SNS for patients with neurogenic constipation may predict about half of those who will have long term benefit from permanent SNS. When other simpler treatments have failed, SNS is a

valuable option. Further research is needed to refinethe factors which might indicate long term benefit through predicting which patients will benefit most.

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Table 1: Outcome scores changes during study phases

	Baseline[5]	SNS - Pre-SNS[6]	Post-treatment - baseline[6]
GA (Constipation)[1]	3.78 (0.64) 16	-1.09 (-1.59 to -0.59) 0.0003	-0.16 (-0.54 to 0.23)
GA (Faecal Incontinence)[1]	1.29 (1.27) 16	-0.17 (-0.54 to 0.20) 0.35	-0.04 (-0.55 to 0.47)
PAC-SYM[1]	1.83 (0.64) 16	-0.73 (-1.06 to -0.39) 0.0003	-0.29 (-0.58 to -0.01) 0.04
Abdominal	2.00 (0.77) 16	-0.84 (-1.27 to -0.40) 0.0009	-0.36 (-0.77 to 0.06)
Rectal	1.38 (0.57) 13	-0.49 (-0.91 to -0.07) 0.026	-0.02 (-0.39 to 0.35)
Stool	2.02 (0.83) 15	-0.65 (-0.90 to -0.40) 0.0001	-0.23 (-0.59 to 0.13)
PAC-QOL[1]	2.26 (0.56) 16	-0.68 (-1.02 to -0.33) 0.0008	-0.10 (-0.35 to 0.16)
Physical Discomfort	2.49 (0.80) 15	-0.74 (-1.14 to -0.35) 0.001	-0.19 (-0.71 to 0.34)
Psychosocial Discomfort	1.77 (0.76) 12	-0.31 (-0.57 to -0.04) 0.027	-0.03 (-0.32 to 0.25)
Worries and Concerns	2.35 (0.73) 16	-0.66 (-1.04 to -0.29) 0.002	-0.15 (-0.47 to 0.18) 0.36
Dissatisfaction	3.04 (0.51) 15	-0.79 (-1.32 to -0.26) 0.006	0.22 (-0.06 to 0.50)
EQ-5D[2]	0.22 (0.27) 15	0.10 (-0.04 to 0.24) 0.16	0.03 (-0.13 to 0.19)
EQ-VAS[2]	45.5 (12.5) 15	2.2 (-9.2 to 13.6) 0.69	-0.5 (-6.1 to 5.2)
Daily Diary[3] (/week) Bowel movements	1.45 (1.52) 16	-0.25 (-0.68 to 0.18) 0.23	
Faecal incontinence episodes	0.86 (2.43) 17	-0.86 (-2.11 to 0.39) 0.16	
Average time spent toileting (minutes)	19.9 (10.5) 16	-6.5 (-12.8 to -0.3) 0.04	
Laxative score	0.10 (0.26) 17	-0.15 (-0.28 to -0.01) 0.03	
Transit Time (hours)[4]	57.3 (17.4) 13	3.9 (-1.0 to 8.8) 0.11	

1 Pre-SNS: Average of score in weeks 1 to 6; SNS: Average of scores in weeks 8 and 9; Post-SNS: Score in week 12

2 Pre-SNS: Average of score in weeks 3 and 6; SNS: Score in week 9; Post-SNS: Score in week 12

3 Pre-SNS: Average of score in weeks 4 to 6; SNS: Average of score core in weeks 8 and 9

4 Pre-SNS: At week 3: SNS: At week 9

5 Mean (SD) N

6 Mean Difference (Confidence Interval) p

Abbreviations

GA: Global Assessment of symptoms.

PAC-SYM: Patient Assessment of Constipation-Symptom score
PAC-QOL: Patient Assessment of Constipation-Quality Of Life score

EQ 5D: European Quality of Life-Five Domain score
EQ-VAS: European Quality of Life-Visual Analogue Score

Table 2: Differences between responders and non-responders to temporary SNS

	N	Non-Responder	Responder	p[1]
Gender: M/F	7/11	1/5	6/6	0.20
Condition: MS/non-MS	11/7	3/3	8/4	0.63
Mobility normal/ restricted/wheelchair	5/5/8	0/3/3	5/2/5	0.052
Age (years)	18	53.7	53.5	0.92
GA Constipation (baserline)	17	4.07	3.68	0.31
PAC SYM (baseline)	17	1.96	1.71	0.75
PAC QOL (baseline)	17	2.57	2.15	0.14
Laxative Score (baseline)	17	0.05	0.10	0.71
Bowel Movement (baseline)	17	1.45	1.64	0.75
Toilet Time (baseline)	17	21.3	22.5	0.75
Stimulation threshold on electrode insertion (milli volts)	11	2.33	2.88	0.51
Transit time (baseline) (hours)	15	50.9	53.2	0.14

1 Continuous variable difference probabilities were estimated using Mann-Whitney U; Gender difference probability estimated using an exact test on counts

Abbreviations
GA Constipation: Global Assessment of Constipation
PAC-SYM: Patient Assessment of Constipation-Symptom score
PAC-QOL: Patient Assessment of Constipation-Quality Of Life score
MS: Multiple Sclerosis
Abbreviations
MS:: multiple sclerosis

Table 3 Differences between responders and non-responders following permanent implantation

		Responder[1]	Non-Responder[1]	Difference	p[2]
Baseline Scores	GA constipation	3.25 (0.52) 6	4.11 (0.63) 6	-0.86	0.03
	PAC-SYM	1.34 (0.38) 6	2.09 (0.45) 6	-0.74	0.01
	PAC-QOL	1.81 (0.39) 6	2.49 (0.50) 6	-0.69	0.025
Stimulation Scores	GA constipation	2.00 (0.63) 6	2.58 (1.11) 6	-0.58	0.37
	PAC-SYM	0.38 (0.14) 6	1.49 (0.86) 6	-1.11	0.006
	PAC-QOL	0.84 (0.43) 6	1.75 (0.88) 6	-0.91	0.11
Long term SNS	GA constipation	1.50 (1.00) 4	4.00 (1.00) 2	-2.50	0.68
	PAC-SYM	0.36 (0.44) 4	1.92 (0.38) 2	-1.56	0.44
	PAC-QOL	0.70 (0.54) 4	2.14 (0.75) 2	-1.44	0.74

1 Mean (SD) N

2 Continuous variable difference probabilities were estimated using Mann-Whitney U

Abbreviations

GA Constipation: Global Assessment of Constipation
PAC-SYM: Patient Assessment of Constipation-Symptom score
PAC-QOL: Patient Assessment of Constipation-Quality Of Life score

Pre-SNS:Baseline
Temporary SNS: during wire stimulation
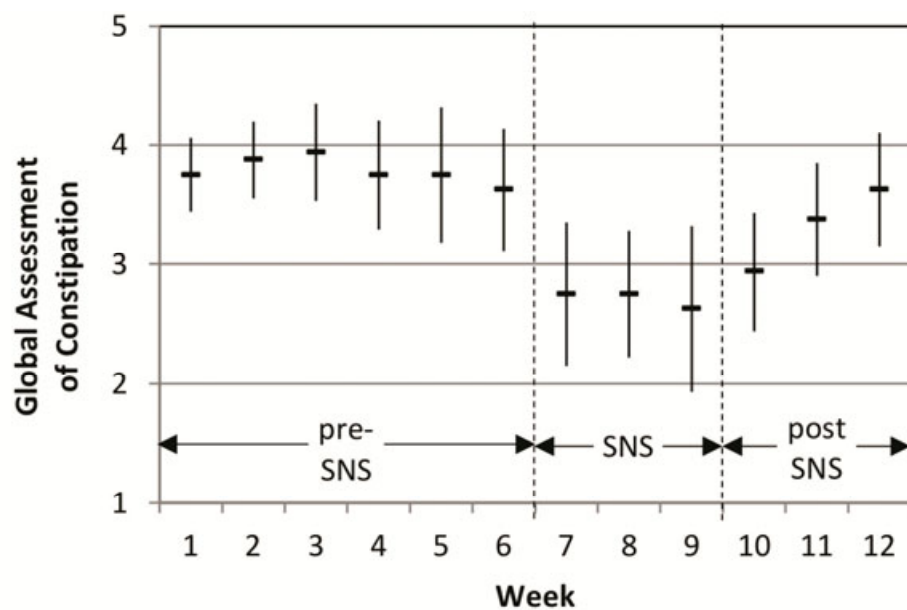Long term SNS: after permanent implant in

responders

Figure 1: Constipation global assessment (GA) scores during the 12 weeks of the study