Sacral nerve neuromodulation for the treatment of lower bowel motility disorders

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ABSTRACT

INTRODUCTION Incontinence and constipation are common and cause a high degree of physical, social and psychological impairment. Maximal conservative therapy may improve some patients but many remain symptomatic. Surgical options are often unsatisfactory, with variable result and further options are limited. Sacral nerve stimulation uses electrical stimulation applied to the sacral nerves, eliciting a physiological effect on the lower bowel, anal sphincter and pelvic floor, resulting in clinical benefit. The objective of this study was to investigate whether sacral nerve neuromodulation can improve patients with disorders of bowel motility, when current maximal treatment has failed and to investigate the underlying physiological mechanism of action.

RESULTS

Incontinence: Nineteen patients, age 58 years (range, 37–71 years), with resistant incontinence for 6 years (range, 2–21 years) underwent stimulation. Continence improved in all at 24 months (range, 3–60 months), fourteen fully continent. Incontinent episodes decreased; 12 (range, 2–30) versus 0 (range, 0–4), $P < 0.001$. Urgency ($P < 0.01$) and quality of life improved ($P < 0.05$). Anal squeeze pressure ($P = 0.001$) and rectal sensation ($P < 0.01$) improved.

Constipation: Four women, (aged 27–36 years) with resistant idiopathic constipation for 8–32 years underwent the first worldwide implants. Symptoms improved in all with temporary, and in three with permanent, stimulation at 8 months (range, 1–11 months). Bowel frequency increased: 1–5 versus 6–28 evacuations/3-weeks. Symptom scores and quality of life improved.

Placebo effect: A double-blind, cross-over study was performed to examine placebo effect and efficacy. Once stimulation was removed, in a blinded manner, symptoms, physiological parameters and quality of life measures rapidly returned to baseline levels.

Autonomic neuromodulation: Sixteen patients, median age 59 years (range, 38–71 years), were studied at 27 months (range, 2–62 years) using laser Doppler flowmetry. Chronic stimulation was at 2.8 V (range, 0.3–3.9 V). Median flux differed between none and chronic stimulation ($P = 0.001$). Step-wise increments caused an immediate, dose-dependent rise in flux ($P < 0.0001$) up to 1.0 V.

CONCLUSIONS This research provides strong evidence that sacral nerve stimulation can improve patients with resistant incontinence and shows proof-of-concept for the treatment of constipation. The effect is unlikely to be due to placebo and the mechanism is rapidly reversible and involves a dose-dependent effect on the autonomic nerves.

KEYWORDS

Sacral nerve stimulation – Neuromodulation – Lower bowel – Motility disorders – Faecal incontinence

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Disorders of lower bowel motility, namely incontinence and constipation, are common and cause a major impact on patient's life-style. Incontinence affects 2% of the general population and up to 10% of the healthy elderly.¹ Estimates of the incidence of constipation range from 3–15%.² Both conditions are initially treated with dietary advice, titrated medication and, if severe, targeted behavioural therapy (biofeedback). While these measures will improve the

majority there remains a significant patient group where treatment fails.

When symptoms are persistent and severe and conservative treatment fails surgery may be considered. Surgery for incontinence has focused on repairing or substituting the anal sphincter, while ignoring the other aspects of the continence mechanism. Overlapping anterior anal sphincter repair is the current first-line option for a disrupted anal

sphincter. Short-term results are good with 70% improved; however, there appears to be a decline with greatly reduced benefit at 5 years.³ In more complex cases, a new sphincter may be constructed – either a biological neosphincter, the dynamic graciloplasty, or an artificial bowel sphincter. While both procedures can restore continence in selected patients, they involve major surgery, have high morbidity and a substantial failure rate.^{4,5} For constipation, surgery involves either a bowel resection, with a low success rate and significant morbidity, or formation of a stoma, which may relieve some symptoms but is often socially unacceptable.⁶ The invasive nature, high morbidity and low success rates of these procedures must be carefully considered when treating this essentially functional condition.

Sacral nerve stimulation (SNS) is a minimally invasive surgical technique that involves low-level chronic electrical stimulation of the nerves of the sacral plexus, producing a physiological effect on the organs innervated by those nerves. While current surgery focuses on structural alteration, SNS has the ability to influence simultaneously the function of all the structures involved in continence or defecation. Through chronic neuromodulation, there is the potential to alter colonic motility, pelvic floor and anal sphincter function and afferent sensation. This represents a completely different approach, with neuromodulation eliciting a clinically beneficial physiological effect. This technique may well be more appropriate when treating a functional condition, often with no associated anatomical abnormality.

The concept of electrical stimulation producing a physiological effect dates back to the beginning of the 19th century; however, the first effective clinical application was used by Brindley with high-voltage stimulation to treat patients with spinal cord injury.⁷ This was then adapted, employing chronic low-level stimulation tolerated in sensate patients, to treat urological dysfunction.⁸ The observation of a beneficial effect on faecal incontinence in patients treated for urological dysfunction, in combination with experimental evidence of colonic activity in spinal patients led to the first implants for bowel dysfunction. Three patients with resistant faecal incontinence were treated successfully with SNS.⁹ Further studies have shown similar improvement.^{10,11}

In a similar manner, it was observed in some of our incontinence patients there was a subjective effect on defecation. Evidence for a possible role in constipation arose initially from urological patients. In a series of 48 patients with co-existing constipation, bowel frequency increased in 78%. Two studies then reported the effects of temporary stimulation. One showed an improvement in 2 of 8 patients,¹² the second showed a subjective improvement.¹³ This led to the first world implants of a sacral nerve stimulator for intractable idiopathic constipation.

The possibility of a placebo effect in this previously unreported benefit for constipation was then investigated. This

question had been previously investigated in a blinded crossover trial in SNS for incontinence, suggesting that a significant placebo effect was unlikely.¹⁴ A double-blind, placebo-controlled, cross-over trial was therefore performed to assess the efficacy and degree of placebo effect in constipation.

Despite definitive clinical benefit, the underlying mechanism of action of SNS remains unclear. There appears to be an effect on multiple nerves within the sacral plexus: The somatic pudendal nerves and direct efferent nerves to the pelvic floor musculature appear to be affected with increased external anal sphincter function. However, studies on the delay between stimulation and effect show a latency 10-times greater than expected, suggesting a more complex, multisynaptic pathway.¹⁵ There appears to be an effect on afferent sensory nerves with heightened sensation yet there is little effect on the intrinsic enteric neurones, the recto-anal inhibitory reflex being unaffected.¹⁵ This, however, is a crude indicator of enteric nerve function, in a nervous system that has the proven ability to adapt and regenerate.

The balance of the autonomic nervous system, the parasympathetic and sympathetic nerves, is the key determinant of colorectal motility and internal sphincter function. Modulation of these nerves may be a major part of the physiological mechanism. Ambulatory manometry has demonstrated a qualitative change in internal anal sphincter and rectal motility with stimulation.¹⁶ Laser Doppler flowmetry is a highly reproducible, gut-specific, quantitative measure of extrinsic autonomic nerve activity.¹⁷ Using this technique, the nature of the effect of SNS on the efferent autonomic nerves was investigated.

Incontinence

Patients and Methods

Nineteen consecutive patients (17 women), median age 58 years (range, 37–71 years), underwent initial temporary stimulation. All had faecal incontinence at least twice per week for 6 years (range, 2–21 years) and had failed to improve with maximal conventional treatment. Aetiology was: obstetric injury ($n = 7$), systemic sclerosis ($n = 4$), idiopathic ($n = 4$), repaired rectal prolapse ($n = 2$), post fistula surgery ($n = 1$) and partial traumatic T2/3 neurological injury ($n = 1$). All patients had at least a demonstrable unilateral pudendal nerve terminal motor latency and in thirteen it was normal bilaterally.

The Harrow Research Ethics Committee granted ethical approval for this and all other studies reported in this paper. All patients gave fully informed written consent.

All patients underwent full clinical assessment, a 3-week bowel habit diary, the SF-36 quality of life assessment, endo-anal ultrasound and anorectal physiological testing including anal manometry and rectal sensation to distension. These were repeated during the last day of temporary

stimulation, (the temporary electrode still *in situ*), and at 3, 6 and 12 months and then annually.

The surgical technique for temporary and permanent sacral nerve stimulation evolved during the study. Percutaneous screening was performed with a helical percutaneous electrode designed to resist dislodgement (Medtronic 3057), which was an initial problem. Subsequently, all permanent implants were performed as a one-stage operation. The latter 10 patients had the impulse generator (Medtronic 3023) placed deep to the fascia in the ipsilateral buttock. This removed the early complication of pain due to the connecting wires from implants placed in the anterior abdominal wall. This also decreased operative time, as there was no requirement to turn and re-drape the patient during surgery.

Statistical analysis was performed with the Wilcoxon paired ranks sum test.

Results

Continence improved in all at median follow-up of 24 months (range, 3–60 months); fourteen patients were fully continent (Table 1). The median episodes of faecal incontinence per week decreased from (pre versus temporary versus permanent stimulation: 12 (range, 2–30) versus 0 (range, 0–7) versus 0 (range, 0–4), $P < 0.001$. Urgency improved in all: the median ability to defer defecation < 1 -min (range, 0–1 min) pre versus 9 min (range, 1–30 min) at longest follow-up ($P < 0.01$).

All temporary percutaneous electrodes were placed as a day-case and screening was performed for a median of 21 days (range, 21–29 days). Permanent implantation was performed at a median of 1 month (range, 0–5 months) after removal of the temporary electrode; in-patient time was 3 days (range, 1–6 days).

There was an overall improvement in quality of life, the SF-36 questionnaire reaching statistical significance ($P < 0.05$) in the role-physical, social function and mental health sub-scales.

Anal manometry showed a significant increase in the median anal squeeze pressure (pre versus temporary versus permanent stimulation: 27 cmH₂O [range, 5–140 cmH₂O] versus 69 cmH₂O [range, 21–160 cmH₂O] versus 55 cmH₂O [range, 7–204 cmH₂O]; $P = 0.001$). Rectal balloon distension elicited a significant change in sensation at initial threshold distension (40 ml air [range, 25–90 ml air] versus 25 ml air [range, 20–65 ml air]; $P < 0.01$) and maximum tolerated volume (125 ml air [range, 70–200 ml air] versus 100 ml air [range, 40–240 ml air]; $P < 0.05$).

There were no major complications, no infections of permanent implants and no implants have had to be removed. One superficial skin infection during percutaneous screening resolved after removal of the temporary electrode and delayed permanent implantation proceeded successfully. There were two lead dislodgements early in the series replaced surgically with good result. Further implants were fixed securely to the periosteum. Patients occasionally

Table 1 The effect of sacral nerve stimulation on continence

Patient	Mean number of episodes of faecal incontinence per week								
	Pre	PNE	Months of follow-up						
			3	6	12	24	36	48	60
1	15	0	0	0	0	0	0	0	0
2	5	0	1	0	2	0	0	0	1
3	20	7	0	0	8	0	0	0	
4	2	0	0	0	0	0	0	0	
5	11	0	0	1	0	0	1		
6	23	2	4	4	7	0			
7	30	2	5	4	7	0			
8	3	0	0	0	0	0			
9	12	2	1	2	6	4			
10	12	1	2	3	0				
11	7	0	1	0	4				
12	29	2	2	2	0				
13	4	0	0	0					
14	7	0	0	0					
15	7	0	0	0					
16	13	0	0						
17	24	1	1						
18	2	0	0						
19	15	0							
Median	12	0***	0***	0***	2**	0**	0*	0	0

*Represents a P -value of < 0.05 with respect to baseline (Wilcoxon Signed Ranks test).

**Represents a P -value of < 0.01 with respect to baseline.

***Represents a P -value of < 0.001 with respect to baseline.

Pre, before stimulation; PNE, percutaneous nerve evaluation.

experienced minor localised electric shocks when passing through ambient electrical or magnetic fields. Deactivation of the pulse generator magnet renders the implant less sensitive and eliminated this problem.

Constipation

Patients and Methods

Four women aged 27–36 years, with severe idiopathic constipation (for 8–32 years, bowel frequency less than twice/week and straining for more than a quarter of the time) who had failed maximal treatment were recruited. All were considering the formation of a colostomy.

Exclusion criteria included previous abdominal surgery, hysterectomy, current or planned pregnancy, anatomical

abnormality on proctography and any significant psychological disturbance or contribution to symptoms (as judged clinically by the investigators).

Correctable causes were excluded via clinical investigation, including colonoscopy and proctography. Whole gut transit time was prolonged in two patients (patients 1 and 2). A 3-week bowel diary, the Wexner constipation score, a symptom analogue score, the SF-36 assessment and anorectal physiological testing were performed at baseline, at the end of 3-weeks of temporary stimulation, 1 month after temporary stimulation before permanent implantation, and at 1, 3 and 6 months after permanent implantation. The transit study was repeated at 6 months.

During all assessment periods, patients were asked not to take laxatives. If absolutely necessary, they were allowed only a 'rescue' laxative of 15 mg oral bisacodyl not more than each third day, recorded in the diary.

The technique for SNS was identical to that previously described with all stimulation parameters set to the same levels. Due to the small number of patients, the results are presented in full, and not statistically analysed.

Results

Percutaneous temporary screening was performed for 21–22 days without complication. Permanent implantation was performed 9 months (range, 1–16 months) after screening as a one-stage procedure, median operative time of 70 min (range, 60–100 min), discharge day 3 (range, days 2–4) without complication.

At longest follow-up (8 months; range, 1–11 months), bowel frequency improved: 1–5 versus 6–28 evacuations/3-weeks (Fig. 1). There was an associated improvement in the evacuation score (4 versus 1), the percentage time with pain and bloating, the Wexner score (22 versus 10) and the patient symptom analogue score (25 versus 83). Quality of life improved in all subscales, except health-transition, with both temporary and permanent stimulation.

Evaluation was continued for the 3-week period after screening following removal of the temporary stimulation wire, prior to permanent implantation. All symptoms, bowel frequency and laxative use returned to baseline levels in this period.

Patient 4 underwent permanent implantation without complication with initial benefit, but was involved in a major road traffic accident one week after surgery. This caused movement of the implanted electrode and a return to baseline levels. This is currently being treated with adjustment of the electrode settings.

All patients used regular laxatives prior to stimulation. During screening, no patient required laxatives and none of the three patients with symptomatic improvement from permanent stimulation required laxatives.

Placebo effect

Patients and Methods

Two female patients aged 36 years with severe, resistant idiopathic constipation who had been implanted with a permanent stimulator 12 months previously were studied (patients 1 and 2 in constipation study). One year was chosen to ensure that the clinical benefit was maintained in the medium-term, and so that the optimal stimulation parameters had been determined.

Three 2-week periods were assessed using bowel diaries, scores, quality of life and anorectal physiology as previously described. The first period was after 1 year of permanent stimulation with the stimulation on. The second and third periods were with the stimulation either on or off, the primary investigator and patient blinded. Both patients used sub-sensory stimulation; thus, neither was aware whether the stimulation was on or off. A clinical scientist controlled the stimulation at each visit using external telemetry. The electrodes were, therefore, undisturbed and the primary investigator blinded.

Table 2 Clinical and physiological results for placebo-controlled cross-over study

Parameter	Patient 1				Patient 2			
	Baseline	1 yr	Stim. off	Stim. on	Baseline	1 yr	Stim. off	Stim. on
Bowel frequency per 2 weeks	1	15	2	10	6	17	4	8
Percentage time with pain and bloating	95%	0%	65%	0%	100%	0%	93%	65%
Wexner constipation score (0–30)	22	4	15	5	20	6	13	13
Symptom analogue score (0–100)	32	94	30	88	28	84	33	60
Anal resting pressure (cmH ₂ O) (NR > 60)	65	82	63	68	84	87	39	84
Anal squeeze pressure (cmH ₂ O) (NR > 60)	32	52	51	41	46	104	57	145
Threshold sensation (ml air) (NR < 45)	45	20	30	20	47	60	40	15
Urge sensation (ml air) (NR < 90)	185	35	60	33	75	75	80	35
Maximum volume (ml air) (NR < 190)	245	65	85	65	143	100	120	70
Anal electrosensation mA (2–9.4)	5.6	4.8	5.4	5.2	7.2	6.0	6.6	5.4
Rectal electrosensation mA (7–36)	29	13	14.5	19	16.2	15	26	12

Results

Clinical benefit appeared to be maintained at 1 year of chronic stimulation compared to baseline results. Once stimulation was removed, in a blinded manner, benefit was rapidly lost with bowel frequency and symptoms returning to baseline levels (Table 2). Quality of life improved with a year of chronic stimulation. There were no complications and both patients rapidly regained their original benefit once stimulation was re-instated.

Autonomic neuromodulation

Patients and Methods

Sixteen patients, 15 women, aged 59 years (range, 38–71 years) who had been successfully treated with permanent SNS for resistant faecal incontinence were studied at 27 months (range, 2–62 months) after implantation. Patients who had undergone a previous bowel resection or who had any evidence of spinal cord injury were excluded as this may potentially disrupt the autonomic innervation.

Laser Doppler flowmetry recordings were performed using a DRT4 laser Doppler flowmeter (Moor Instruments, Devon, UK) and an endoscopic probe (DP6A), of end diameter 1 mm² on an out-patient basis.¹⁷ Initial measurements were recorded at the level of chronic stimulation that the patient derived clinical benefit. Stimulation was then turned off and the change in flux recorded. Measurements were then repeated with step-wise 0.1-V increments in stimulation amplitude up to 1 V and then at 2, 3, 4 and 5 V. Stimulation was ceased if painful as this may cause autonomic arousal. Frequency and pulse width remained constant at 14 Hz and 210 µs.

Statistical analyses were performed for the grouped blood flux data using the Wilcoxon paired ranks test comparing no stimulation with baseline chronic stimulation, and at each separate level of acute stimulation. An analysis of variance model and regression analysis was also performed.

Results

There were no complications, and no patient experienced a decrease in symptomatic benefit due to the Doppler recording and temporary alteration of stimulation levels.

The rate of change of blood flux in response to changes in stimulation amplitude occurred within seconds and steady state readings were always reached within 1 min.

The median level for chronic stimulation was 2.8 V (range, 0.3–3.9 V). The median flux with chronic stimulation was 869 flux units (range, 507–989 flux units). When stimulation was removed, flux dropped rapidly to 545 flux units (range, 355–887 flux units); $P = 0.001$. Step-wise 0.1-V increments caused a rapid rise in flux between zero and 1.0 V (Fig. 2). Further increments did not result in further significant increases in flux ($P > 0.1$). Analysis of variance showed a significant difference in flux between different voltage levels ($P < 0.0001$), and regression analysis showed that flux increased as a function of voltage ($P < 0.0001$).

Discussion

This research has demonstrated unequivocally that sacral nerve stimulation can improve patients with disorders of lower bowel motility when conventional treatment has failed.

At time of submission, this was the largest reported series for patients with faecal incontinence treated with SNS. All patients had symptoms severe enough to consider

Figure 2 Change in grouped laser Doppler flux in response to amplitude of stimulation. Analysis of variance, $P < 0.001$; regression analysis, $P < 0.001$.

a colostomy and had failed all other conventional treatment. Dramatic clinical benefit appears to be maintained, without deterioration, in the medium-term with an associated improvement in quality of life. Subsequent reports have confirmed this clinical benefit and have emphasised the safety of this procedure.^{10,11} NICE guidelines have been issued for 2005 confirming the safety and efficacy of sacral nerve stimulation for faecal incontinence, leading the way for SNS to be performed as a main-stream treatment when conservative treatment fails, rather than restricted to the research arena alone.

The surgical technique has evolved during this research to avoid temporary screening lead dislodgements and pain with permanent implants. Temporary screening offers a minimal morbidity, pain-free, day-case technique for predicting success prior to any invasive surgery. This is extremely rare in any surgical technique and is a major advantage of SNS. The positive predictive value of temporary SNS appears to approach 100%, with subsequent failures normally due to poor placement of the definitive electrode.

The definitive implant is a relatively minor procedure with low morbidity, especially compared to alternative surgical options. The operative site is distant from the bowel so previous procedures do not complicate surgery. With a one-stage implant, 1 month after temporary stimulation, the infection risk appears to be low and this is the author's current technique. Variations have been employed, particularly the use of a percutaneously tunnelled screening electrode that is later permanently implanted, which may lead to a higher infection rate. The development of a 'tyned' percutaneously placed permanent electrode has allowed more recent, unreported implants to be

performed percutaneously.¹⁸ This allows implantation of a permanent SNS to become a day-case procedure.

The physiological mechanism of action is currently unclear but SNS has the potential to affect all of the structures involved in continence and defecation. This may be the reason that it appears to have clinical superiority over other techniques that address one aspect only, normally the anal sphincter. The study on constipated patients showed a marked improvement in three of four patients in the short term. While this is pilot data only, it has shown proof-of-concept that SNS can produce clinical benefit when other treatments have failed in this multifactorial condition. This work has led to the design and development of a currently running international multicentre trial for SNS in constipation in eight European centres.

The cross-over trial indicated that this previously unreported beneficial clinical effect is unlikely to be due to placebo. The rapid loss of benefit once stimulation was removed, after a year of successful treatment, suggests that constant stimulation is required and that the underlying mechanism is a rapidly reversible neurological mechanism. This finding agrees with a previous similar study in patients treated with SNS for incontinence.¹⁴ However, the numbers were small, due to limited numbers of patients who have clinical benefit at sub-sensory stimulation levels. Further larger studies would be indicated.

While the precise physiological mechanism is unclear, there is evidence that all aspects of the sacral nerve plexus are affected: The most consistent finding is a modest increase in external anal sphincter function, modulated through the efferent somatic nerve fibres.^{10,11} The effect on sensation appears

less clear; however, this research and other larger studies have suggested altered rectal sensation.¹⁵ This paper reports the first attempt to examine the autonomic nerves directly and illustrated a rapidly reversible, dose-dependent effect up to a threshold of 1.0-V. This finding may have implications for the level of future therapeutic stimulation. It is likely that chronic SNS produces the observed beneficial clinical effect through modulation of all of these nerve fibres. The relative contribution of each and the central effects on higher centres remain unknown and an area for future research.

The cost of this treatment should be considered and is approximately £7000. This is not inexpensive; however, it is comparable to other surgical procedures, and has a far higher success rate and lower morbidity. Compared to conservative long-term bowel care, SNS reaches financial advantage after 5 years.¹⁹

Conclusions

Overall, there is little doubt that sacral nerve stimulation can dramatically improve patients with faecal incontinence when other treatments have failed. There is a possibility the same may be true for resistant idiopathic constipation but the current data are too sparse to support this fully. The mechanism of action is neurological in basis but the precise nature remains to be elucidated. However, it has been a personal privilege to be in the right place at the right time in order to be allowed to take this treatment from research into current specialised colorectal clinical practice.

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