REVIEW ARTICLE

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Systematic review of the impact of sacral neuromodulation on clinical symptoms and gastrointestinal physiology

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The full paper (including Tables 1 and 3 and reference section) can be accessed online at http://onlinelibrary.wiley.com/doi/10.1111/ans.13257/abstract

Key words
anorectal physiology, faecal incontinence, sacral nerve stimulation, sacral neuromodulation.

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This paper was presented in part at the Surgical Research Society 50th Annual Meeting, November 2013, Adelaide, SA, Australia.

Accepted for publication 9 June 2015.

doi: 10.1111/ans.13257

Abstract

Background: Sacral neuromodulation (SNM) has emerged as a treatment option for faecal incontinence (FI). However, its objective effect on symptoms and anorectal function is inconsistently described. This study aimed to systematically review the impact of SNM on clinical symptoms and gastrointestinal physiology in patients with FI, including factors that may predict treatment outcome.
Methods: An electronic search of MEDLINE (1946–2014)/EMBASE database was performed in accordance with PRISMA guidelines. Articles that reported the relevant outcome measures following SNM were included. Clinical outcomes evaluated included: frequency of FI episodes, FI severity score and success rates. Its impact on anorectal and gastrointestinal physiology was also evaluated.
Results: Of 554 citations identified, data were extracted from 81 eligible studies. Meta-analysis of the data was precluded due to lack of a comparison group in most studies. After permanent SNM, 'perfect' continence was noted in 13–88% of patients. Most studies reported a reduction in weekly FI episodes (median difference of the mean −7.0 (range: −24.8 to −2.7)) and Wexner scores (median difference of the mean −9 (−14.9 to −6)). A trend towards improved resting and squeeze anal pressures and a reduction in rectal sensory volumes were noted. Studies failed to identify any consistent impact on other physiological parameters or clinicophysiological factors associated with success.
Conclusion: SNM improves clinical symptoms and reduces number of incontinence episodes and severity scores in patients with FI, in part by improving anorectal physiological function. However, intervention studies with standardized outcome measures and physiological techniques are required to robustly assess the physiological impact of SNM.

Introduction

Community studies conducted in Australia[1,2] and New Zealand[3] have identified faecal incontinence (FI) in approximately 11% of subjects, meaning that 3 million people across the two nations suffer with this condition. However, its true prevalence is likely to be higher, as it remains an underdiagnosed problem.[4] Furthermore, up to 40% of sufferers report severe impact on quality of life and emotional well-being.[5] Until recently, surgical treatment of this condition was limited to a few (often morbid) procedures with limited long-term success.[6] However, sacral neuromodulation (SNM) has provided an additional option for sufferers since 1995.[7]

SNM is based on the premise that stimulation of the sacral nerves will restore full continence or markedly improve symptoms. However, its true clinical efficacy in large samples of patients and the rates of perfect continence achieved remains uncertain. Similarly, the mechanism of action of SNM remains unclear. Previously, the implicit assumption[7] was that SNM exerted its effect via augmentation of anal pressures. However, given its efficacy in patients with sphincter defects, its action is likely to be, at least in part, extrasphincteric. Indeed, the possibility of central neuromodulation via spinal afferent fibres has been suggested.[8] Over the past two decades, several systematic reviews[8–11] have been performed on this topic. However, some contain important limitations due to small

sample size[9,12] and inclusion and analysis of disparate studies of variable quality.[13] Therefore, the aim of this study was to provide a comprehensive and contemporary systematic review of the published studies on the impact of SNM on clinical outcomes (subjective and objective) and gastrointestinal (i.e. anorectal, colonic, small bowel and gastric) physiology in patients with FI. In addition, studies were reviewed for factors/clinicophysiological parameters associated with clinical success both in the short (trial phase) and long term.

Methods

A systematic review of SNM for FI was performed by conducting an electronic search of MEDLINE database (1946–November 2014) in accordance with the PRISMA guidelines.[14] The search keywords used (and combined using Booleans operators) included: electrical stimulation therapy, electric stimulation, sacral nerve, sacral nerve stimulation, sacral nerve modulation, sacral neuromodulation, faecal incontinence, fecal incontinence, soiling, bowel dysfunction, bowel seepage, defecation, anal canal, anal incontinence, constipation, evacuatory dysfunction, gastrointestinal motility, gastric emptying, small intestine and urinary incontinence. In addition, the Cochrane Database and Embase (1966–2014) were also searched for relevant articles. The reference lists of all included articles were also scrutinized for relevant studies.

Inclusion criteria

All published studies reporting clinical or physiological outcomes after SNM for FI performed in adults were included. All eligible studies required an intervention in the form of either percutaneous nerve evaluation (PNE, i.e. the trial phase) and/or permanent implantation. Eligible articles also included those analysing clinicophysiological factors that were associated with success or failure of SNM for FI. Patients with scleroderma were also included as such patients were often included in studies.

Exclusion criteria

Studies where SNM was performed for urinary incontinence, constipation/evacuatory dysfunction and FI secondary to organic pathologies (e.g. complete spinal cord injury, cauda equina syndrome, congenital anorectal abnormalities, Crohn's disease and radiation proctitis) were excluded. Technical studies, or those where non-standard SNM parameters were used or where patients had tried other forms of sacral neuromodulation (e.g. transcutaneous), were also excluded. Non-English studies, abstracts, non-peer reviewed studies, commentaries, letters or records where baseline data for the patients were not provided for analysis and those where outcomes of interest were not reported were also considered ineligible. Furthermore, studies performed on rectal tissue or blood flow and those performed on animals were also excluded.

Study quality assessment

As most studies were published case series, quality assessment was assessed using the National Institute for Health and Care Excellence, Quality Assessment for Case Series (QACS) tool (http://www.nice.org.uk/guidance/cg3/resources/appendix-4-quality-of-case-series-form2) by scoring the studies out of a maximum of eight. A study scored 1 point each if (i) it was multicentre; (ii) hypothesis/aim/objective were clearly reported; (iii) outcomes were defined; (iv) inclusion and exclusion criteria were stated; (v) data were collected prospectively; (vi) patients were recruited consecutively and (vii) the main findings of the study were clearly described; and (viii) outcomes were stratified.

Study outcomes

Clinical outcomes of interest included: (i) improvement in symptoms reported in the form of bowel chart diary (FI episodes over a period of time); (ii) changes in objective and validated FI severity scores using either Wexner/Cleveland[15] or Vaizey/St Marks[16] scoring systems; (iii) overall rate of success (defined as >50% improvement in FI symptoms compared with baseline); and (iv) proportion of subjects who achieved perfect continence. This overall success rate, while somewhat arbitrary, has recently been endorsed in a consensus statement[17] and validated in a study of patients with FI.[18] It is based on observation of an improvement in FI symptoms using symptom diaries kept by the patient before and during intervention. Symptoms evaluated include: number of incontinence episodes, faecal urgency, use of pads and impact on lifestyle. Other definitions and outcomes used in this review included: (i) intention-to-treat (ITT) analysis, which is based on measuring outcome based on the number of patients initially enrolled in the treatment as opposed to (ii) per protocol analysis (PPA), which only measures the final outcome based on the number of patients who had a successful PNE and then went on to receive a permanent implant. Primary failure is defined as those who never had a clinical response to PNE, while secondary failure, refers to those patients who had a successful response to PNE but failed to subsequently achieve therapeutic benefit from the permanent implant. Physiological outcomes of interest included: (i) anorectal, specifically anal pressures (maximum resting and squeeze pressure (mmHg)); (ii) rectal sensory thresholds (balloon volumes in millilitres of air or water), where all reported pressures in cmH_2O were converted to mmHg; (iii) small/large bowel motility; and (iv) gastric emptying. Additionally, clinicophysiological factors associated with a successful response to SNM were determined.

Data extraction

Quantitative data were extracted by two independent reviewers (NM/YS) and results were cross-checked. Any discrepancies in results were resolved by repeat data extraction, discussion and further review of the index study.

Data analysis

Given the variable reporting of results (in means and medians) and/or the fact that majority of studies lacked a control group, meta-analysis of the data was precluded. As such, the results from each study are presented in a summarized and aggregate form. Summary results were reported as the median value of the mean differences or the median value of the median differences for each outcome (e.g. FI episodes, Wexner incontinence severity scores, anal pressures and rectal balloon volumes) pre and post SNM.

Results

The initial electronic search revealed 552 citations. Two additional articles were identified using the EMBASE search engine.[19,20] The

title and abstract of each were screened and ineligible studies were excluded. Full-text review and cross-reference check was then performed on 91 citations (Fig. 1), which identified 81 citations eligible for inclusion in this study. For studies where multiple publications were performed on the same cohort of patients, the shortest and the longest follow-up results of these cohorts were included.[21,22]

Study characteristics and limitations

Only one randomized trial[23] and two cross-over studies[24] were identified with all remaining studies comprising of prospective case series ($n = 42$), retrospective case series ($n = 14$), cross-sectional ($n = 2$) and one experimental design (Table 1, Table S1). The median QACS score for study quality was 5 (range 3–8). Most of the studies were European ($n = 71$) followed by equal number of publications from Australia and the United States. The sample size and follow-up periods were heterogeneous with a median sample size of 27 (range 2–200) and a median follow-up period of 23 months (range 2 weeks–118 months). The majority of the patients participating in the studies were female (median percentage of 90.5%).

Impact on clinical outcomes

Clinical outcome data were obtained from 63 studies. Large variability in reporting of outcomes was found with results presented as means, medians and incontinence episodes over a variable number of weeks reported (Table 1, Table S1). Forty studies reported outcomes using objective incontinence severity scores, with the vast majority using the Cleveland Clinic (Wexner) score, although six studies used the Vaizey/St Mark's scoring system and two applied other measures. Eighteen studies reported rates of 'perfect continence'.

Overall, there was improvement in subjective and objective measures of FI across all studies, irrespective of study design. FI episodes per week was used as an outcome measure in 23 studies, FI episodes per 2 weeks in seven studies, per 3 weeks in 10 studies and per day in two studies. Among the studies reporting on weekly incontinence rate, the median reduction of the mean and the median value of FI episodes was 7.0 (range 2.7–24.8) and 8 (range 3–13.3), respectively (Table 1, Table S1). Similarly, there was improvement in objective FI severity scores with a median of the mean and median reduction in the Wexner scores across the 32 studies being 9 (range 6–14.9) and 8 (2.4–14), respectively. The PNE success rate, defined as >50% reduction in clinical symptoms over the evaluation period, ranged from 51.5 to 100%, with a median value of 81% on a per protocol basis. The reported rates of 'perfect continence' ranged from 13 to 88% (Table 2). Notwithstanding the inevitable heterogeneity of patient characteristics, pooling of these results ($n = 608$) gave a perfect continence rate of 36.5% on an ITT basis and 42.9% on a PPA.

The only prospective randomized study compared best conservative management to SNM in 120 patients over a period of 12 months and conclusively demonstrated the clinical efficacy of the treatment arm with improvement in subjective and objective measures of FI.[23] Similarly, Leroi *et al.*,[47] in a randomized case cross-over study of 24 patients, reported significant improvement in clinical symptoms during the stimulation period. The only other case cross-over study by Vaizey *et al.*[24] was limited by its small sample size of $n = 2$.

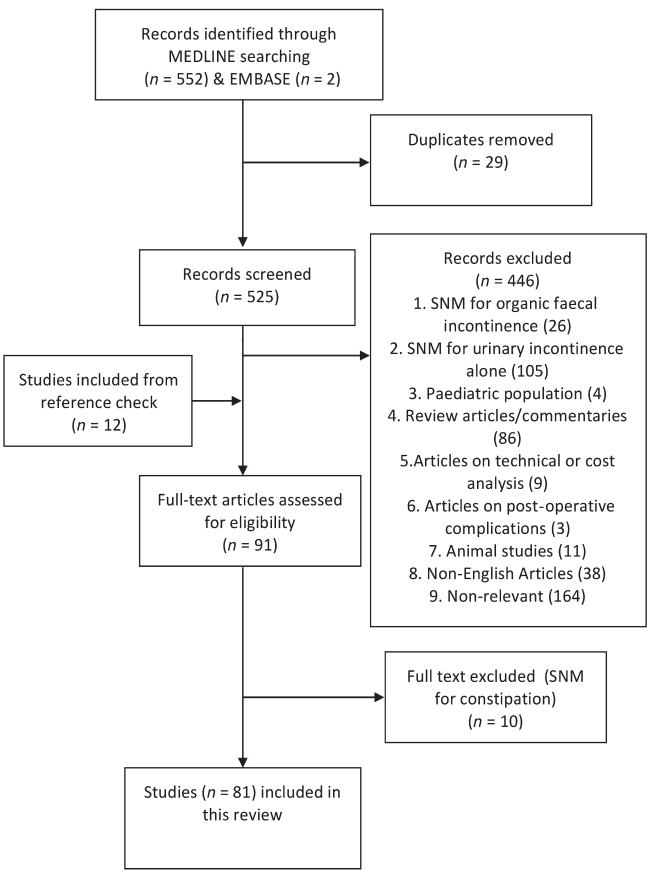

Fig 1. Flow chart of the systematic review process as per PRISMA 2009 guidelines.

Impact on gastrointestinal physiology

Anorectal

The impact on anorectal physiological parameters was reported in 37 studies (Table 3, Table S2). The methodological heterogeneity of techniques used and measurements recorded during anorectal manometry was a significant issue when summarizing data. However, a consistent trend was noted in most studies, with an increase in both maximum resting pressure and squeeze pressure after SNM with a median difference of the mean of 5.9 (−11.8–21) and 14.8 mmHg (−12.5–96), respectively (Table 3). No correlation could be made between manometric findings and clinical symptoms after stimulation as most results were not grouped based on outcome. Rectal sensitivity, as measured by the volume required to elicit sensory thresholds, tended to improve (as evidence by a reduction in sensory threshold volumes) after SNM. The median reduction of the mean values for sensory volumes was 11.9, 16.4 and 6.6 mL for first sensation, sensation of urge and maximum tolerated volume, respectively (Table 3). The median values are shown in Table S2. The effect of SNM on rectal compliance was measured in seven studies,[25,29,35,44,55,58,59] but none of these showed any statistically significant changes, although the sample size in each study was small ranging from 11 to 23 patients. Other rectal physiological parameters such as rectal stool retention test, rectoanal angle and rectal motility was not affected by SNM.[59,60] However, Michelsen *et al.*[61] demonstrated a significant decrease in postprandial rectal tone during stimulation.

Table 2 Details of patients achieving full continence in 18 studies

Study identification	Sample size (*n*)	Number responding to sacral neuromodulation (*n*)	Number achieving full continence (*n*)	% Full continence (per protocol)
Leroi *et al.*†[47]	34	34	5	15
Leroi *et al.*[35]	9	8	1	13
Altomare *et al.*†[26]	52	38	9	24
Oom *et al.*[77]	46	37	8	22
Boyle *et al.*[48]	50	37	13	35
Hull *et al.*[22]	72	64	26	41
Oz-Duyos *et al.*[49]	47	28	14	50
Matzel *et al.*[36]	37	37	12	32
Jarret *et al.*[50]	59	46	19	41
Tjandra *et al.*[23]	59	54	25	46
Ganio *et al.*[30]	25	22	11	50
George *et al.*[51]	25	23	12	52
Matzel *et al.*[7]	3	3	2	67
Santoro *et al.*[52]	28	28	19	68
Kenefick *et al.*[53]	15	15	11	73
Kenefick[54]	19	19	14	74
Ganio *et al.*[29]	19	17	14	82
Vaizey *et al.*[55]	9	8	7	88
Total	**608**	**518**	**222**	**Pooled‡: 36.5%** **Range: 13–88%‡**

†Data after permanent implant only. ‡Intention-to-treat analysis (patient with perfect continence/total sample size). Per protocol analysis = 42.9%.

Other gastrointestinal organs

Two studies investigated the impact of SNM on gastric motility and emptying rate.[62,63] In both studies, a randomized cross-over design was employed but only one was double-blinded.[63] A washout period of 1 week was used in one[62] and not the other. No consistent changes were observed in gastric motility and emptying or small bowel motility during stimulation as assessed using a magnetic tracking system and scintigraphic methods. No consistent impact of SNM on colonic transit was identified in the three studies that investigated its effect in patients with FI.[63,64,65] Baseline data were available only in the studies by Michelsen *et al.*[64] and Uludag *et al.*,[65] whereas Damgaard *et al.*[63] turned off the stimulator in a randomized cross-over design. Michelsen *et al.* showed that colonic transit times were increased after SNM and that there was a decrease in antegrade transport from the ascending colon and an increase retrograde transport from the descending colon. Similarly, Patton *et al.*[42] used high-resolution colonic manometry and observed that SNM alters colonic motility by increasing retrograde propagating sequences in the left colon.

Factors associated with successful clinical response to SNM

Fourteen studies sought to determine factors predictive of outcome following subchronic (PNE) and chronic stimulation using Interstim pulse generators (IPGs) (Table S3). The factors investigated varied across studies but included (i) patient factors, such as baseline demographics (age, sex, body mass index, baseline quality of life scores) and anorectal physiological parameters (anal resting and squeeze pressures, anal electrosensation, rectal sensation, pudendal nerve terminal motor latency, anal electromyography); (ii) disease factors, such as aetiology and severity of incontinence and previous treatments (e.g. biofeedback); (iii) technical factors, such as type of leads, site of insertion, intraoperative motor and sensory responses and stimulation parameters. Only a small number of factors were associated with outcome and are shown in Table S3. Notably, age was a significant variable in more than one study[66,67] and the younger the patient (<70 years old), the more likely a successful response to SNM, although Feretis *et al.*[19] found that older age was associated with success. Anal sphincter defects and multiple PNE procedures were correlated with failures of SNM in two studies.[68,69] The variables that were not predictive of outcome included (not shown in table): baseline anorectal physiological parameters and colonic transit study, body mass index, gender, stimulation parameters, aetiology of FI (idiopathic versus organic), baseline quality of life, duration and severity of FI and presence of anxiety or depression. The primary and secondary failure rates of SNM across these studies were 31.5 and 17.4%, respectively.

Discussion

SNM has been used extensively in the management of FI over the past 20 years. In this systematic review, the impact of SNM on clinical symptoms and objective FI severity scores was investigated in the summative data analysis. Generally, most studies were of poor quality (case series) with only one randomized controlled trial and two cross-over studies; the sample sizes and follow-up periods were heterogeneous. The median reduction of FI episodes per week was 7–8 (2.7–24.8) and objective FI score (Wexner) was 8–9 (2.5–14.9). Overall, the PNE success rate ranged from 51.5 to 100%, with a median value of 81%. Of the patients who responded to the trial phase, up to 43% achieved full continence, at least in the short term. The impact of SNM on anorectal physiology was variable. However, there appeared to be a trend towards improved anal pressures (as evidenced by increased resting and maximum squeeze pressures) and rectal sensitivity (as evidenced by a decrease in sensory threshold volumes). However, no consistent changes on other rectal or other gastrointestinal physiological parameters were evident and no robust clinical or physiological factors were identified that could reliably predict success following SNM, although the age of the patient and the integrity of the anal sphincter complex may be of importance.

The clinical efficacy of SNM as shown in this review is similar to other systematic reviews.[13] The median reduction of FI episodes per week reported by Thin *et al.*[11] was 7, consistent with the findings of

the present review. The use of FI severity scores is able to more objectively assess the impact of SNM on clinical symptoms. All but six studies used the Cleveland Clinical (Wexner) FI scores for this purpose and significant reductions in scores were evident, suggesting objective clinical improvement. However, this scoring system does not incorporate improvement in symptoms of faecal urgency or reduction in use of constipating medications and may underestimate the clinical efficacy of SNM. Furthermore, FI is a complex disorder with varied symptom repertoire. Accordingly, current measures to assess outcome (including the Wexner incontinence score) may not be sophisticated enough to comprehensively assess outcome. Moreover, they may fail to capture how patients change their lifestyles to manage their symptoms (e.g. being close to the toilet).

In terms of the impact of SNM on anorectal physiology, this review was able to demonstrate a trend towards an increase in anal pressures and improved rectal sensation (reduced sensory threshold volumes), consistent with other studies.[13] Increasingly, rectal reservoir dysfunction is appreciated as an important factor in the development of FI.[70] Traditionally, patients with FI are frequently noted to have rectal hypersensitivity (heightened awareness of distension) and are only able to tolerate small volumes during rectal distension.[71] However, rectal hyposensitivity, which by contrast is characterized by reduced awareness of distension and the ability to tolerate large volumes during rectal distension, is also considered important in the pathophysiology of FI in some patients.[72,73] The fact that this review identified a tendency for rectal sensory threshold volumes to decrease rather than increase following SNM suggests that reduced sensory threshold volumes (i.e. rectal hypersensitivity) was not the predominant abnormality in the patients selected for SNM in the majority of studies. However, patients were not stratified on the basis of rectal sensory function in most studies and thus further evaluation is required before any definitive conclusions can be drawn. This may be pertinent as patients with abnormal rectal sensitivity are likely to demonstrate a favourable response to SNM.[74] The studies assessing rectal compliance before and after SNM revealed no significant differences following SNM, suggesting that modulation of afferent nerve pathways rather than alteration of rectal biomechanics may account for the changes in rectal sensitivity noted.[75]

The influence of SNM on the colon, small bowel and stomach has been explored in several studies. Although no consistent impact was noted on gastric emptying or small bowel motility, such studies have suffered from small sample sizes, lack of baseline data and the possibility of carry over effect upon turning the stimulation off.[62,63] The impact of SNM on colonic motility deserves further evaluation in future studies, as several studies have noted a decrease in antegrade activity originating in the ascending colon and an increase in retrograde activity from the descending colon.[42,64] Consequently, it has been suggested that this change in colonic activity following SNM creates a 'physiological brake' that prevents the delivery of stool to the (functionally suboptimal) anorectal unit and thus reduces incontinent episodes.

Despite multiple studies exploring various factors, prognostic indicators of success remain elusive. In fact, the most recent publication exploring this question in 60 patients[76] including the randomized study by Tjandra *et al.*[23] failed to identify any factors predictive of outcome. Currently, the response observed during the trial stimulation (PNE) is most useful in predicting outcome following insertion of the permanent implant. However, the rate of secondary failure of up to 17%, as seen in this review, suggests that the response to the trial stimulation does not predict long-term outcome when faced with a progressive disease such as FI. Other significant factors associated with therapeutic long-term outcomes across the studies included young age at implant, improvement in symptoms of faecal urgency, neurogenic FI, a loose stool consistency at baseline, low threshold stimulation voltage, more severe FI and low rectal perception volume to urge.

The studies included in this systematic review are limited by their quality and are subject to publication bias (in favour of publishing positive results only). However, performing double-blinded, randomized crossover studies to evaluate SNM in a large sample is difficult for various reasons: (i) after insertion of the implant, optimization of stimulation parameters is often necessary to establish efficacy; (ii) blinding is challenging as most patients are aware when they are being 'stimulated', even at subsensory levels; (iii) the 'carry over' effect of SNM has not extensively been explored; and (iv) patient recruitment is difficult as most patients are reluctant to participate in a trial involving 'sham' stimulation with risk of symptom deterioration/recurrence. Accordingly, well-planned long-term observational studies may provide useful contributions to the literature on the topic. Lack of a meta-analysis further reduced the quality of the quantitative analysis provided in this review. Although Tan *et al.*[13] performed a comprehensive meta-analysis in 2011 of various outcomes of SNM, the appropriateness is questionable as a meta-analysis of data points from case series compromises the accuracy of the results.

In conclusion, despite the poor quality of studies published, SNM appears to be clinically efficacious with up to 42% achieving full continence and the majority experiencing improvement in symptoms. Its impact on gastrointestinal physiology remains poorly understood and thus there is a need for more robust scientific investigations on the mechanism of action of SNM and its predictive factors. Given the low morbidity, reversibility and minimal invasiveness of this procedure, the results provided by SNM therapy supersedes other surgical interventions for FI.

Acknowledgements

NM is supported by the National Health and Medical Research Council Postgraduate and Royal Australasian College of Surgeons Foundation of Surgery Research Scholarships.

Supporting information

Additional Supporting Information with further references may be found in the online version of this article at the publisher's web-site:

Table S1 Impact of sacral neuromodulation on clinical outcomes (median values).

Table S2 Impact of sacral neuromodulation on anorectal physiology (median values).

Table S3 Significant factors associated with sacral neuromodulation clinical outcome.