World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i41.7048

World J Gastroenterol 2013 November 7; 19(41): 7048-7054
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Neuromodulation for fecal incontinence: An effective surgical intervention

Giuseppe Chiarioni, Olafur S Palsson, Corrado R Asteria, William E Whitehead

Giuseppe Chiarioni, Division of Gastroenterology of the University of Verona, Valeggio s/M Hospital, Azienda Ospedaliera Universitaria Integrata di Verona, 37067 Valeggio sul Mincio, Verona, Italy
Giuseppe Chiarioni, Olafur S Palsson, William E Whitehead, Division of Gastroenterology and Hepatology and Center for Functional Gastrointestinal and Motility Disorders, University of North Carolina at Chapel Hill, Chapel Hill, NC 27516, United States
Corrado R Asteria, Department of Surgery and Orthopedics, General Surgery Unit, Azienda Ospedaliera Carlo Poma di Mantova, Asola General Hospital, 46041 Asola, Mantova, Italy
Author contributions: Chiarioni G, Palsson OS and Whitehead WE contributed equally to the conception, design and drafting of the manuscript; Asteria CR provided criticism and suggestion of high intellectual content.
Supported by National Institute of Diabetes and Digestive and Kidney Disease Grant, No. R01 DK031369
Correspondence to: Giuseppe Chiarioni, MD, Division of Gastroenterology of the University of Verona, Valeggio s/M Hospital, Azienda Ospedaliera Universitaria Integrata di Verona, 37067 Valeggio sul Mincio, Verona, Italy. chiarioni@tin.it
Telephone: +39-45-6338548 Fax: +39-45-6338696
Received: June 27, 2013 Revised: August 16, 2013
Accepted: August 28, 2013
Published online: November 7, 2013

Abstract

Fecal incontinence is a disabling symptom with medical and social implications, including fear, embarrassment, isolation and even depression. Most patients live in seclusion and have to plan their life around the symptom, with secondary impairment of their quality of life. Conservative management and biofeedback therapy are reported to benefit a good percentage of those affected. However, surgery must be considered in the non-responder population. Recently, sacral nerve electrostimulation, lately named neuromodulation, has been reported to benefit patients with fecal incontinence in randomized controlled trials more than placebo stimulation and conservative management, by some unknown mechanism. Neuromodulation is a minimally invasive procedure with a low rate of adverse events and apparently favorable cost-efficacy profile. This review is intended to expand knowledge about this effective intervention among the non-surgically skilled community who deals with this disabled group of patients.

Key words: Fecal incontinence; Neuromodulation; Sacral nerve stimulation; Biofeedback; Anal sphincter

Core tip: This review summarizes the evidence for neuromodulation of fecal incontinence. Neuromodulation is effective for some patients with fecal incontinence of different etiology unknown mechanism; when analyzed by intent to treat analysis, the median responder rate is 59%. The most common serious adverse event is infection at the site of implant which occurs in about 3% of patients. Cost of treatment is high relative to conservative treatment and biofeedback but seems to be cost-effective when offset by gains in quality-adjusted years. Randomized controlled trials comparing neuromodulation with biofeedback therapy in fecal incontinence are advisable to tailor patients' management.

Chiarioni G, Palsson OS, Asteria CR, Whitehead WE. Neuromodulation for fecal incontinence: An effective surgical intervention. *World J Gastroenterol* 2013; 19(41): 7048-7054 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i41/7048.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i41.7048

INTRODUCTION

Fecal incontinence (FI) is defined as the accidental loss of solid or liquid stools and is a common disabling condition that is often under-reported at medical consultation

because of fear and embarrassment. In a recent study of > 1500 primary care patients, FI was self-reported by 36.2% of patients, but only 2.7% of them had a medical diagnosis of FI[1]. FI has a significant impact on quality of life (QOL) and health expenditure and may facilitate the placement of older patients in nursing home facilities[2]. Therefore, increased medical screening of FI is needed because both conservative and interventional treatments are available. Biofeedback therapy to increase rectal awareness of stools and ameliorate anal sphincter response improved continence in about two-thirds of patients in open and randomized controlled trials (RCTs)[3,4]. However, patients with severe impairment of rectal sensation and/or previous anal trauma do poorly with biofeedback, and alternative options are desirable in selected patients[5]. In the past a number of surgical procedures has been proposed to treat FI. Major drawbacks were the small sample sizes and potential worsening of incontinence[6]. Sacral nerve electrostimulation, later also called neuromodulation (NRM), was first applied in 1995 by Matzel *et al*[7] with encouraging results in a small group of patients with FI without evidence of anal sphincter defects. The technique was attractive because of its limited side effects and for being minimally invasive. Since then, the effectiveness of NRM in improving FI has been proven in a number of studies, although its mechanism of action remains ill defined[8]. However, physicians involved in the treatment of disordered anal continence should consider NRM among potential treatment options, and this review is intended to be a primer for the non-surgical community.

Search methods

Search terms were fecal incontinence OR anal incontinence and sacral nerve stimulation OR neuromodulation. These searches were limited to human subjects, adults, and studies published in full in the English language between January 1995 and December 2012. Case reports, preliminary studies, and small sample series investigating < 15 patients were not considered. Databases searched were PubMed, Web of Science, Cochrane Reviews, and Embase. The bibliographies of identified studies were also searched for additional references. To address NRM effectiveness, special consideration was given to RCTs and adequately powered prospective trials.

TECHNIQUE, SAFETY AND MECHANISM OF ACTION OF NRM

Technique

NRM is a minimally invasive surgical intervention consisting of: (1) a testing evaluation interval; and (2) a second stage with permanent stimulator implantation, provided the testing interval results are clinically successful. The first stage, also termed percutaneous nerve evaluation (PNE), is of most relevance to determine the feasibility of electrode implantation into the sacral foramina, and to demonstrate clinical benefits worth pursuing with permanent NRM[9]. Two technical options are available for PNE: a temporary, percutaneously placed, unipolar stimulation lead to be later removed, or the surgical placement of a quadripolar lead next to a target nerve[9]. Both types of leads are then connected to an external pulse generator to be substituted by a permanent pulse generator implanted subcutaneously in case of positive outcome. The permanent implant sized a quarter dollar or 2 euro coin (diameter 24.26 mm, thickness 1.75 mm) is commonly placed in the gluteal area and can be managed by a small handheld device[9]. A small retrospective study evaluated outcome and complications of the two PNE techniques[10]. No difference in outcome was shown, but the infection rate was slightly higher in patients undergoing surgical placement.

Safety

The commonest adverse events are implant site pain and paresthesia, which is seen in up to 28% of patients in some large series with careful reporting about safety[11,12]. Pain is usually managed conservatively and explant of the device is rarely needed. However, a recent meta-analysis concluded that incidence of implant site pain may be as low as 6%[8]. The most serious complication is infection at the implant site, which was seen in up to 10.8% in the largest series of > 100 patients[11,12]. The control of site infection may require device explant in approximately half of those affected[12]. The meta-analysis by Tan *et al*[8] supports diverse evidence indicating that the typical infection rate is 3%, with the proportion requiring the device to be removed for refractory infection being about 3% of those infected. Additional side effects reported in < 8% of patients are urinary incontinence, diarrhea, and extremity pain, which always resolve spontaneously or are effectively managed by medication[8]. In older series, broken or displaced electrodes occurred in about 4% of cases[8], and sometimes required device explantation. However, this problem is becoming less frequent since the electrodes were redesigned. Battery replacement is usually required after a median of 7 years[13].

Mechanism of action

In 1999, Vaizey *et al*[14] first reported the effect of NRM on anorectal physiology measured by 24-h solid state catheter manometry in a small group of 10 patients with FI. Resting anal pressure did not change significantly and some evidence of modification of rectal sensitivity and tone was observed. The authors speculated that NRM worked via complex neuromodulation of sacral reflexes to regulate rectal sensitivity and anorectal motility[14]. Since then, several studies focused on modifications of anorectal physiology associated with NRM in FI, with conflicting results. In their meta-analysis, Tan *et al*[8] concluded that NRM is associated with improvement in anal canal pressure at rest and with voluntary squeezing, and a decrease in the maximum tolerable rectal volume. However, subsequent studies had inconsistent results, with RCTs and long-term studies failing to show a rel-

evant influence of NRM on anal pressure[15,16]. When there are significant improvements in anal canal pressure, the size of the effect is small and the final resting and squeeze pressures appear to be below the normal range for healthy controls[8]. This is not commensurate with the large clinical effects seen for FI and suggests that the mechanism by which NRM improves continence is not primarily an improvement in anal canal pressure. This issue was addressed in a recent review by Gourcerol *et al*[17], which specifically focused on defining the potential mechanism of action of NRM. The authors speculated on three potential mechanisms: (1) somatovisceral reflex; (2) modulation of the perception of afferent information; and (3) increase in external anal sphincter activity[17]. However, no definitive evidence could be found to support any of these and a multifactorial component was further speculated to justify the efficacy of NRM. The authors concluded that NRM is effective almost certainly *via* modulation of spinal and/or supraspinal afferent inputs, but many gaps remain in the understanding of the mechanism of action of NRM[17].

EFFECTIVENESS

RCTs

After the early report of Matzel *et al*[7], a number of trials were developed to evaluate the efficacy of NRM in FI[7,8]. A major drawback to assessing this literature is the huge variance in inclusion and outcome criteria and follow-up intervals[8]. Additional limitations are small sample size (often < 20 patients) and lack of adequate control groups[8]. However, the majority of uncontrolled trials reported a favorable outcome in more than two-thirds of patients with limited side-effects. Researchers were unable to identify any clinical and/or functional variable that could predict outcome[8]. In earlier reports, patients were selected on findings of either no or marginal evidence of anal sphincter defects. However, this limitation was later dropped because of the unclear definition of the mechanism of action of the treatment[8]. In 2005, Leroi *et al*[18] reported on the first randomized, controlled, double blind, multicenter study testing the efficacy of NRM in FI and/or severe urgency of any etiology. Patients with an ultrasound diagnosis of sphincter defect were included, provided the defect was not considered to be the main determinant of incontinence[18]. After implantation, 27 of 34 patients with FI were randomized in a double-blind crossover manner to NRM active treatment (electrostimulator ON) *vs* placebo (electrostimulator OFF) for a 1-mo period with the device *in situ*. A final interval of 3 mo was also included in the evaluation with patients still blinded, potentially choosing either the ON or the OFF modality[18]. Twenty-four patients completed the trial, making the sample underpowered. However, patients reported a significant improvement in both symptoms and QOL scores, and anal physiology when in active treatment compared to placebo, providing evidence that a placebo effect was not the main determinant of NRM outcome[18]. However, until recently, NRM was not compared to conservative management (diet, lifestyle modification, constipating drugs, and biofeedback), which is cheaper, commonly available, and often associated with benefits in at least 50% of patients with FI[3]. Tjandra *et al*[15] randomized 120 patients with FI to either supervised optimal medical therapy or NRM. Conservative treatment included bulking agents, pelvic floor exercises, or lifestyle and dietary manipulations, but it did not include biofeedback[15]. NRM was significantly more effective in improving frequency of incontinence with 25 patients regaining perfect continence[15]. Cleveland Clinic Continence Score and QOL score were both significantly improved as well[15].

Open label trials and meta-analysis

In a recent prospective, open label, multicenter trial, Wexner *et al*[11] confirmed the effectiveness of NRM in improving FI in a large sample of 120 patients with 112 of them undergoing permanent implantation. The vast majority of patients (83%) reported significant improvement of FI according to the outcome measurement selected, including 41% gaining complete anal continence, after a mean follow-up of 28 mo[11]. FI is a chronic disorder, therefore, Mellgren *et al*[12] reported on the same cohort after a mean follow-up of 3.1 years (range: 0.2-6.1 years) with at least a partial data set available in 64% of the patients. A significant decrease in episodes of incontinence was still reported by 86% of available patients with 41% regaining continence. A stable improvement in QOL score was also reported by patients[12]. To deepen the analysis, a carried forward observation at 3 years was performed showing a 78% success rate. However, the success rate dropped to 59% at 3 years when considering all missing data as failures[12]. Historically, anal sphincter disruption has been considered a contraindication to perform NRM, which was not even considered in the presence of a relevant morphological alteration[7-9]. However, Chan *et al*[19] provided sound evidence against this assumption in a comparative cohort study. The effectiveness of NRM in improving FI and QOL at 1 year was not significantly different in 21 patients with a disrupted external anal sphincter (81% persisting after previous sphincter repair) when compared to the outcome of 32 patients with FI and an intact anal sphincter[19]. These data were confirmed by an RCT comparing NRM with conservative treatment in which many patients with defects in both the internal and external sphincters were included, showing that NRM was equally effective in those with or without sphincter disruption[15]. The therapeutic potential of NRM compared to conservative treatment in FI has also been reported in several, mostly small studies including patients with distinct pathological conditions, including rectal resection and pelvic irradiation[8,20,21]. In these distinct conditions dealt with in the following section, FI response rates may be lower, with about 50% of patients responding to temporary stimulation[20,21]. A recent meta-analysis by Tan *et al*[8] reported on a total of

Table 1 Effectiveness of neuromodulation in fecal incontinence

Ref.	Sample	Study design	Major findings	Adverse events	Comments
Tjandra *et al*[9]	120 patients with severe FI (solid or liquid FI > 1/wk) were randomized to 2 groups. Of 60 randomized to test stimulation, 53 received permanent implants. Average age 63 yr; > 90% female. Sphincter defect or scar in 47% of both groups	Single site RCT comparing NRM to optimal medical management	71% of permanently implanted patients (63% of randomized patients – ITT analysis) reported > 50% reduction in FI episodes/wk at 12 mo. FI episodes/wk decreased from 9.5 to 3.1 in SNS group, and not at all in controls. All 4 QOL domains significantly improved in SNS. Anal squeeze pressure was unchanged. SNS significantly different from control on all outcomes	Pain in 6%, seroma in 2%, and excessive tingling in vaginal region in 9%, but no septic complications	Low complication rate and excellent outcomes may be related to this being a single-site study
Wexner *et al*[11]	Multicenter study. 133 received test stimulation; 120 (90.2%) qualified for permanent implant. Average age 60.5 yr; 92% females. Inclusion required > 2 solid or liquid accidents/wk for > 6 mo and > 12 mo postpartum	Multicenter cohort study in United States, Canada, and Australia. Hypothesis was that > 50% would report > 50% reduction in FI frequency at 12 mo compared to baseline. QOL and safety were secondary endpoints	73% of permanently implanted patients (66% of all undergoing test stimulation – ITT analysis) showed > 50% reduction in FI episodes/wk at 12 mo. FI episodes/wk decreased from 9.4 at baseline to 1.9 at 12 mo. All 4 domains of the FI QOL improved significantly. An IAS defect predicted poorer outcome	Pain in 25.8%, paresthesia in 12.5%, infection in 10.8%	
Mellgren *et al*[12]	See Wexner (2010). 77 patients completed the 36 mo FU assessment	This reports the 36 mo outcomes for the Wexner (2010) study	At 36 mo, 86% of 77 patients available for assessment, but only 55% of 120 enrolled patients, reported > 50% reduction in FI	Pain in 28%, paresthesia in 15%, infection in 10%. 5/120 required device explant and 2 required device replacement	ITT analysis under-estimates efficacy because some patients were lost to FU for reasons unrelated to efficacy
Michelsen *et al*[16]	177 patients at single Danish hospital. Average age 60. 142 (80%) had positive PNE and 126 received NRM	Uncontrolled case series	In 107 of 111 who still had stimulator in place at 12 mo, Wexner score decreased in 87 (median decrease of 7) and was unchanged or worse in 20. No significant change in anorectal manometry	15 of 126 with permanent implant had device explanted. There were 2 infections requiring explant	ITT analysis was not possible. Many patients were lost to FU
Hollingshead *et al*[13]	118 patients received PNE, 91 (77%) qualified for NRM; and 86 received NRM	Uncontrolled case series	For all 86, median FI episodes/wk decreased from 8.5 to 1.3 and Wexner score decreased from 15 to 9. In 16% of patients reporting 50% reduction initially, efficacy was lost at median of 11.5 mo	Broken leads in 2. Battery replacement in 7 at mean of 81 mo. No other AEs reported	ITT analysis not possible
Altomare *et al*[23]	94 patients from 6 hospitals underwent PNE, and 60 qualified for and underwent NRM. Average age 58 yr, 83% female	Uncontrolled case series	Of 60 implanted, 2 died (unrelated) and 6 had devices explanted, leaving 52 for 5 year FU. At 5 yr, 37 (39% by ITT) had > 50% decrease in FI frequency. Squeeze and resting pressures increased, maximum tolerated volume decreased	AEs in 8 patients: electrode displacement in 8; pain in 3, allergic reaction in 1; myocardial infarct in 1; unrelated death in 2	ITT success rate at 5 yr was 40% after adjustment for 2 unrelated deaths
Muñoz-Duyos *et al*[24]	Spanish study of 47 patients who received PNE, of whom 29 (62%) received NRM. PNE was ineffective in 16 and 3 had technical failures	Uncontrolled case series with median 3 yr FU. Cost analysis was primary focus	At last FU, 14 were continent and 11 had > 50% reductions in FI frequency. QOL significantly improved. Total direct costs for NRM were €371 434, estimated to be €16 181 per quality adjusted life year. No improvement in anal canal pressures	8 patients experienced pain but none required explantation	ITT response rate was 53.2%
Dudding *et al*[22]	British study of 70 patients who received PNE, of whom 61 had > 50% reduction. At analysis, 51 had received permanent implants, and FU was available for 48. These patients may also be included in the Hollingshead (2011) report	Uncontrolled case series with median 24 mo FU. Primary focus was cost-effectiveness. Direct and indirect costs were estimated by theoretical model of services required rather than on actual costs	At 2 yr FU, 41 of 48 with long-term FU (85.4%) had >50% reduction. Direct costs were estimated at £9795 for SNS compared to £2529 for conservative treatment. The estimated incremental cost- effectiveness ratio was £25 070, which is convenient, being within £30 000 recommended by United Kingdom national guidelines	10/48 had complications including 2 wound infections, 1 lead migration, 5 pain, 2 device failures	ITT response rate was 58.6%. Cost analysis was based on theoretical/ imputed data rather than real costs

Chan *et al*[19]	60 consecutive patients underwent PNE and 53 received NRM. These were separated into 21 with EAS defect *vs* 32 with intact EAS. One surgeon did all surgeries	Prospective cohort study comparing those with EAS defect to those with intact sphincter	There was a trend for patients with EAS defect to have worse incontinence and poorer squeeze pressures at baseline and FU, but not significant. Outcomes were similar: At 12 mo FU 68.8% with sphincter disruption vs 72.0% with intact sphincter had > 50% reduction in FI. No differences in anal manometry or QOL outcomes	Seroma in 1/53; pain in 3/53. No AEs required explant	Strong support for hypothesis that NRM is equally effective in patients with EAS defects. ITT responder rate for combined group was 63%
Michelsen *et al*[28]	20 patients randomized; 19 had complete data	Randomized prospective crossover comparing NRM continuously for 3 wk to NRM on only during waking hours for 3 wk	Wexner and St Mark's incontinence scores and frequency of soiling were significantly worse during device off period. However, FI frequency was not significantly different between conditions	AEs were not reported	Not directly relevant to efficacy of NRM
Leroi *et al*[18]	34 consecutive FI patients (31 females) considered, 27 eventually studied, 24 completed the trial	Randomized, double-blind, crossover, controlled trial. All 27 patients underwent NRM then randomized in a double-blind crossover design to stimulator ON vs stimulator OFF for 1-mo interval. Patients while blinded choose to meet the final period of 3 mo ON or OFF	Cleveland Clinic Continence score, frequency of FI and urgency, delay in postponing defecation, subjective feeling of improvement, anal physiology, QOL score all significantly improved in the ON interval compared to the OFF interval	10 out of initial 34 reported AE, 4 device explantations: 3 for pain and 1 for infection	First RCT to show effectiveness of NRM compared to placebo; underpowered sample

AE: Adverse event; EAS: External anal sphincter; FU: Follow-up; IAS: Internal anal sphincter.

994 patients undergoing NRM with 665 permanently implanted, confirming significant improvement in symptoms and QOL in patients with FI. A disrupted anus was not the main determinant of outcome[8]. However, some criticisms of NRM outcome reports should be considered (Table 1). Outcomes for NRM are often expressed as the proportion of patients receiving a permanent implant who continue to have at follow-up assessment a > 50% reduction in FI relative to baseline[8,11,12]. However, this likely overestimates the efficacy of NRM compared to other treatments (*e.g.*, biofeedback therapy), where it is conventional to report effectiveness in terms of an intention-to-treat (ITT) analysis[3]. To calculate the ITT response rate, one must include in the denominator all patients who received test stimulation (PNE). When this is done (Table 1), the responder rate ranges from 40% to 66%, with a median of 59%, compared to a median of 85% when only those who received a permanent implant were included in the denominator[11,22,23]. In addition, some large studies did not provide the data to calculate the ITT responder rate[13,16]. The response to PNE ranges from 64% to 96.7%, with a median of 87%, and 10 reporting at least a 50% reduction in FI from baseline[8,22-24]. In a recent Danish study, a questionnaire was mailed to 127 patients with FI and ongoing NRM, to assess subjective patient satisfaction and frequency of incontinence, and 85% responded[25]. A total of 57.3% of the responders reported positively about NRM treatment[25]; a percentage close to the calculated ITT response rate. In addition, satisfaction with treatment was closely related to pretreatment frequency of incontinence; namely, the more incontinent the patient, the more likely to report treatment dissatisfaction[25]. Finally, the effects of NRM are well sustained with 75% of those treated still reporting > 50% symptom reduction at about 7 years[26]. In a separate study, Uludağ *et al*[27] reported that 84% were still reporting > 50% reduction in FI at 7 years. Switching off the sacral nerve stimulator at night might reduce the device-associated cost, but it is likely associated with a poor long-term outcome[28].

Distinct and rare conditions

The efficacy of NRM has also been investigated under several distinct and rare conditions associated with FI, including: (1) double incontinence; (2) rectal resection; (3) pelvic radiotherapy; (4) anal sphincter atrophy; and (5) spinal lesions. In these conditions, FI is commonly deemed unresponsive to conservative treatment and poorly amenable to surgical intervention[2,3]. These conditions have mostly been studied in case reports and small case series of NRM of FI with encouraging results, but no adequately powered RCTs[9]. Notwithstanding that NRM to treat FI was developed by sporadic observations of symptom benefit in urinary urge incontinence, few studies have addressed the bene-

fit of NRM in double incontinence[9]. Caremel *et al*[29] first reported on clinical questionnaires sent to 57 patients with double incontinence treated by permanent implantation, with FI as the main indication for NRM in 60% of them. About two-thirds of patients responded, with 49% reporting an improvement in both fecal and urinary incontinence. Patients implanted for urinary incontinence as the main indication were more likely to report full amelioration of both types of incontinence[29]. Recently, Faucheron *et al*[30] reported a single-center study of 57 patients (54 women) who underwent PNE and permanent implantation for double incontinence of multiple etiology, with a median follow-up of 62.8 mo. Improvement in both fecal and urinary incontinence was evaluated by dedicated scores, with about 50% of patients reporting amelioration of both symptoms[30]. Surprisingly, bladder-related clinical improvement scored slightly lower than bowel-related improvement. Re-intervention rate (29%) and complication rate (12%) were both relatively high[30]. Rectal resection for cancer and pelvic radiotherapy are conditions commonly associated with secondary severe alterations in bowel compliance[3]. Incontinence is predominant at night and mostly deemed incurable[2,3]. Two European groups investigated the efficacy of NRM in these hard-to-treat conditions in small samples. Both studies reported PNE to be effective in improving continence in approximately half of those treated, but the efficacy of permanent implantation was not reported[20,21]. Atrophy of the anal sphincter is an additional hard-to-treat FI disease for which NRM has been associated with clinical benefit in open trials. Santoro *et al*[31] have reported a single-center study of 28 patients with magnetic-resonance-imaging-documented external anal sphincter atrophy of different severity undergoing permanent implantation for FI. A significant improvement in both FI and QOL scores was reported regardless of severity of sphincter atrophy[31]. This study provided indirect evidence of improvement in anal sphincter function as the mechanism of action of NRM[31]. Finally, a few studies have evaluated the efficacy of NRM for loss of normal bowel function due to nerve injury, neurological disease, or congenital defects of the nervous system - so-called neurogenic bowel. Holzer *et al*[32] assessed clinical outcome in a cohort of 29 patients undergoing permanent implantation for FI of mixed neurological etiology, including diabetes. The authors claimed that most patients were symptomatically improved, but outcome parameters were ill defined[32]. Recently, an Italian group reported on the efficacy of NRM in improving symptoms of pelvic floor dysfunction in 23 patients with incomplete spinal cord damage[33]. A significant improvement in FI was found in the majority of patients, but the grouping of patients with both constipation and FI made it hard to interpret the results[33].

COST

The cost of NRM is high when compared to conservative medical management, pelvic floor exercises and biofeedback therapy. Actual cost of NRM varies widely among countries as well as health insurance conditions. However, studies from three different countries have concluded that NRM is cost-effective when offset by the quality-adjusted life-years gained, and that it is likely to be reimbursed by government health programs[22,24,34,35].

CONCLUSION

In conclusion, NRM is effective for FI of diverse etiology. Encouraging results have also been reported for FI therapy in distinct and rare conditions, but RCTs are lacking and no firm conclusion can be actually drawn. NRM is reported to have long-term benefit in more than two-thirds of patients with FI undergoing permanent implantation, by some as-yet-unknown mechanism. However, when analyzed by ITT analysis, the median responder rate drops to 59% of those treated. NRM is a minimally invasive procedure. The most common serious adverse event is infection at the site of implantation, which occurs in about 3% of cases and requires device explantation in about 3% of all patients receiving permanent implants. Cost of treatment is high relative to that of conservative treatment and biofeedback but there are studies from different countries suggesting that NRM is cost-effective when offset by gains in quality-adjusted life years. However, RCTs comparing NRM to biofeedback therapy for FI are required to resolve this issue.

REFERENCES

1 **Dunivan GC**, Heymen S, Palsson OS, von Korff M, Turner MJ, Melville JL, Whitehead WE. Fecal incontinence in primary care: prevalence, diagnosis, and health care utilization. *Am J Obstet Gynecol* 2010; **202**: 493.e1-493.e6 [PMID: 20223447 DOI: 10.1016/j.ajog.2010.01.018]

2 **Miner PB**. Economic and personal impact of fecal and urinary incontinence. *Gastroenterology* 2004; **126**: S8-13 [PMID: 14978633 DOI: 10.1053/j.gastro.2003.10.056]

3 **Chiarioni G**, Ferri B, Morelli A, Iantorno G, Bassotti G. Biofeedback treatment of fecal incontinence: where are we, and where are we going? *World J Gastroenterol* 2005; **11**: 4771-4775 [PMID: 16097042]

4 **Heymen S**, Scarlett Y, Jones K, Ringel Y, Drossman D, Whitehead WE. Randomized controlled trial shows biofeedback to be superior to pelvic floor exercises for fecal incontinence. *Dis Colon Rectum* 2009; **52**: 1730-1737 [PMID: 19966605 DOI: 10.1007/DCR.0b013e3181b55455]

5 **Chiarioni G**, Bassotti G, Stanganini S, Vantini I, Whitehead WE. Sensory retraining is key to biofeedback therapy for formed stool fecal incontinence. *Am J Gastroenterol* 2002; **97**: 109-117 [PMID: 11808933 DOI: 10.1111/j.1572-0241.2002.05429.x]

6 **Michot F**, Costaglioli B, Leroi AM, Denis P. Artificial anal sphincter in severe fecal incontinence: outcome of prospective experience with 37 patients in one institution. *Ann Surg* 2003; **237**: 52-56 [PMID: 12496530 DOI: 10.1007/DCR.0b013e3181e19d68]

7 **Matzel KE**, Stadelmaier U, Hohenfellner M, Gall FP. Electrical stimulation of sacral spinal nerves for treatment of faecal incontinence. *Lancet* 1995; **346**: 1124-1127 [PMID: 7475602 DOI: 10.1016/S0140-6736(95)91799-3]

8 **Tan E**, Ngo NT, Darzi A, Shenouda M, Tekkis PP. Meta-

analysis: sacral nerve stimulation versus conservative therapy in the treatment of faecal incontinence. *Int J Colorectal Dis* 2011; **26**: 275-294 [PMID: 21279370 DOI: 10.1007/s00384-010-1119-y]
9 **Tjandra JJ**, Lim JF, Matzel K. Sacral nerve stimulation: an emerging treatment for faecal incontinence. *ANZ J Surg* 2004; **74**: 1098-1106 [PMID: 15574154 DOI: 10.1111/j.1445-1433.2004.03259.x]
10 **Dudding TC**, Parés D, Vaizey CJ, Kamm MA. Comparison of clinical outcome between open and percutaneous lead insertion for permanent sacral nerve neurostimulation for the treatment of fecal incontinence. *Dis Colon Rectum* 2009; **52**: 463-468 [PMID: 19333047 DOI: 10.1007/DCR.0b013e318197e31f]
11 **Wexner SD**, Coller JA, Devroede G, Hull T, McCallum R, Chan M, Ayscue JM, Shobeiri AS, Margolin D, England M, Kaufman H, Snape WJ, Mutlu E, Chua H, Pettit P, Nagle D, Madoff RD, Lerew DR, Mellgren A. Sacral nerve stimulation for fecal incontinence: results of a 120-patient prospective multicenter study. *Ann Surg* 2010; **251**: 441-449 [PMID: 20160636 DOI: 10.1097/SLA.0b013e3181cf8ed0]
12 **Mellgren A**, Wexner SD, Coller JA, Devroede G, Lerew DR, Madoff RD, Hull T. Long-term efficacy and safety of sacral nerve stimulation for fecal incontinence. *Dis Colon Rectum* 2011; **54**: 1065-1075 [PMID: 21825885 DOI: 10.1097/DCR.0b013e31822155e9]
13 **Hollingshead JR**, Dudding TC, Vaizey CJ. Sacral nerve stimulation for faecal incontinence: results from a single centre over a 10-year period. *Colorectal Dis* 2011; **13**: 1030-1034 [PMID: 20718837 DOI: 10.1111/j.1463-1318.2010.02383.x]
14 **Vaizey CJ**, Kamm MA, Turner IC, Nicholls RJ, Woloszko J. Effects of short term sacral nerve stimulation on anal and rectal function in patients with anal incontinence. *Gut* 1999; **44**: 407-412 [PMID: 10026329 DOI: 10.1136/gut.44.3.407]
15 **Tjandra JJ**, Chan MK, Yeh CH, Murray-Green C. Sacral nerve stimulation is more effective than optimal medical therapy for severe fecal incontinence: a randomized, controlled study. *Dis Colon Rectum* 2008; **51**: 494-502 [PMID: 18278532 DOI: 10.1007/s10350-007-9103-5]
16 **Michelsen HB**, Thompson-Fawcett M, Lundby L, Krogh K, Laurberg S, Buntzen S. Six years of experience with sacral nerve stimulation for fecal incontinence. *Dis Colon Rectum* 2010; **53**: 414-421 [PMID: 20305440 DOI: 10.1007/DCR.0b013e3181ca7dc2]
17 **Gourcerol G**, Vitton V, Leroi AM, Michot F, Abysique A, Bouvier M. How sacral nerve stimulation works in patients with faecal incontinence. *Colorectal Dis* 2011; **13**: e203-e211 [PMID: 21689312 DOI: 10.1111/j.1463-1318.2011.02623.x]
18 **Leroi AM**, Parc Y, Lehur PA, Mion F, Barth X, Rullier E, Bresler L, Portier G, Michot F. Efficacy of sacral nerve stimulation for fecal incontinence: results of a multicenter double-blind crossover study. *Ann Surg* 2005; **242**: 662-669 [PMID: 16244539 DOI: 10.1097/01.sla.0000186281.09475.db]
19 **Chan MK**, Tjandra JJ. Sacral nerve stimulation for fecal incontinence: external anal sphincter defect vs. intact anal sphincter. *Dis Colon Rectum* 2008; **51**: 1015-124; discussion 1015-124; [PMID: 18484136 DOI: 10.1007/s10350-008-9326-0]
20 **Maeda Y**, Høyer M, Lundby L, Buntzen S, Laurberg S. Temporary sacral nerve stimulation for faecal incontinence following pelvic radiotherapy. *Radiother Oncol* 2010; **97**: 108-112 [PMID: 20570003 DOI: 10.1016/j.radonc.2010.12.004]
21 **de Miguel M**, Oteiza F, Ciga MA, Armendáriz P, Marzo J, Ortiz H. Sacral nerve stimulation for the treatment of faecal incontinence following low anterior resection for rectal cancer. *Colorectal Dis* 2011; **13**: 72-77 [PMID: 19843119 DOI: 10.1111/j.1463-1318.2009.02066.x]
22 **Dudding TC**, Meng Lee E, Faiz O, Parés D, Vaizey CJ, McGuire A, Kamm MA. Economic evaluation of sacral nerve stimulation for faecal incontinence. *Br J Surg* 2008; **95**: 1155-1163 [PMID: 18581439 DOI: 10.1002/bjs.6237]
23 **Altomare DF**, Ratto C, Ganio E, Lolli P, Masin A, Villani RD. Long-term outcome of sacral nerve stimulation for fecal incontinence. *Dis Colon Rectum* 2009; **52**: 11-17 [PMID: 19273950 DOI: 10.1007/DCR.0b013e3181974444]
24 **Muñoz-Duyos A**, Navarro-Luna A, Brosa M, Pando JA, Sitges-Serra A, Marco-Molina C. Clinical and cost effectiveness of sacral nerve stimulation for faecal incontinence. *Br J Surg* 2008; **95**: 1037-1043 [PMID: 18574847 DOI: 10.1002/bjs.6140]
25 **Duelund-Jakobsen J**, van Wunnik B, Buntzen S, Lundby L, Baeten C, Laurberg S. Functional results and patient satisfaction with sacral nerve stimulation for idiopathic faecal incontinence. *Colorectal Dis* 2012; **14**: 753-759 [PMID: 21883814 DOI: 10.1111/j.1463-1318.2011.02800.x]
26 **Matzel KE**, Lux P, Heuer S, Besendörfer M, Zhang W. Sacral nerve stimulation for faecal incontinence: long-term outcome. *Colorectal Dis* 2009; **11**: 636-641 [PMID: 18727721 DOI: 10.1111/j.1463-1318.2008.01673.x]
27 **Uludağ O**, Melenhorst J, Koch SM, van Gemert WG, Dejong CH, Baeten CG. Sacral neuromodulation: long-term outcome and quality of life in patients with faecal incontinence. *Colorectal Dis* 2011; **13**: 1162-1166 [PMID: 20955512 DOI: 10.1111/j.1463-1318.2010.02447.x]
28 **Michelsen HB**, Krogh K, Buntzen S, Laurberg S. A prospective, randomized study: switch off the sacral nerve stimulator during the night? *Dis Colon Rectum* 2008; **51**: 538-540 [PMID: 18299927 DOI: 10.1007/s10350-008-9219-2]
29 **Caremel R**, Damon H, Ruffion A, Chartier-Kastler E, Gourcerol G, Michot F, Menard JF, Grise P, Leroi AM. Can sacral neuromodulation improve minor incontinence symptoms in doubly incontinent patients successfully treated for major incontinence symptoms? *Urology* 2012; **79**: 80-85 [PMID: 22099864 DOI: 10.1016/j.urology.2011.06.013]
30 **Faucheron JL**, Chodez M, Boillot B. Neuromodulation for fecal and urinary incontinence: functional results in 57 consecutive patients from a single institution. *Dis Colon Rectum* 2012; **55**: 1278-1283 [PMID: 23135587 DOI: 10.1097/DCR.0b013e31826c7789]
31 **Santoro GA**, Infantino A, Cancian L, Battistella G, Di Falco G. Sacral nerve stimulation for fecal incontinence related to external sphincter atrophy. *Dis Colon Rectum* 2012; **55**: 797-805 [PMID: 22706133 DOI: 10.1097/DCR.0b013e3182538f14]
32 **Holzer B**, Rosen HR, Novi G, Ausch C, Hölbling N, Schiessel R. Sacral nerve stimulation for neurogenic faecal incontinence. *Br J Surg* 2007; **94**: 749-753 [PMID: 17410558 DOI: 10.1002/bjs.5499]
33 **Lombardi G**, Del Popolo G, Cecconi F, Surrenti E, Macchiarella A. Clinical outcome of sacral neuromodulation in incomplete spinal cord-injured patients suffering from neurogenic bowel dysfunctions. *Spinal Cord* 2010; **48**: 154-159 [PMID: 19668257 DOI: 10.1038/sc.2009.101]
34 **Ratto C**, Litta F, Parello A, Donisi L, Doglietto GB. Sacral nerve stimulation is a valid approach in fecal incontinence due to sphincter lesions when compared to sphincter repair. *Dis Colon Rectum* 2010; **53**: 264-272 [PMID: 20173471 DOI: 10.1007/DCR.0b013e3181c7642c]
35 **Indinnimeo M**, Ratto C, Moschella CM, Fiore A, Brosa M, Giardina S. Sacral neuromodulation for the treatment of fecal incontinence: analysis of cost-effectiveness. *Dis Colon Rectum* 2010; **53**: 1661-1669 [PMID: 21178862 DOI: 10.1007/DCR.0b013e3181f46309]

P- Reviewer: Santoro GA **S- Editor**: Song XX **L- Editor**: Kerr C
E- Editor: Zhang DN

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327