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Sacral neuromodulation for faecal incontinence following obstetric sphincter injury – outcome of percutaneous nerve evaluation

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Each author is accountable for all aspects of the work and for ensuring that questions related to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. Each author has final approval of the version to be published. In addition, the contribution of each author is as follows:

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Abstract

Aim

The purpose of this study was to assess the efficacy of percutaneous nerve evaluation (PNE) in women with faecal incontinence (FI) following obstetric anal sphincter injury and relate the outcomes to baseline factors with special emphasis on the extent of sphincter defect.

Method

This was a prospective study at a tertiary colorectal referral unit at the University Hospital of North Norway conducted from 2012-2014. Sixty-three women underwent a three–week PNE using a tined lead and the Verify® external neurostimulator. The primary outcome was efficacy defined as the percent of reduction in weekly FI episodes, and patients with 50% or more reduction were defined as responders. Baseline factors affecting the primary outcome were explored. Sphincter defects were classified with a validated 3D endoanal ultrasound defect score.

Results

Fifty-six (89%) of the 63 women were responders with a reduction in weekly FI episodes of 94.5%, from median (interquartile range) 4.8 (2.0-11.0) to 0.5 (0-2.0, $p<0.001$). Twenty-nine (52%) reported no weekly FI episodes, and urgency episodes disappeared in 18 (32%). In the multivariable linear regression model, efficacy was related to concomitant urinary incontinence ($p=0.04$), body mass index (BMI) ($p=0.03$) and pain during PNE ($p=0.046$) but not to the extent of sphincter defect ($p= 0.1$). Responders had a higher St. Mark's score than non-responders ($p=0.046$).

Conclusions

The vast majority of women had successful PNE tests. Responders had higher baseline St. Mark's scores than non-responders. Efficacy was related to concomitant urinary incontinence, BMI and pain, not to the extent of sphincter defect.

What does this paper add to the literature?

In this large, prospective series of women with faecal incontinence following obstetric anal sphincter injury, the majority had a successful outcome of PNE using a tined lead and the Verify® neurostimulator. Efficacy was related to concomitant urinary incontinence, body mass index and pain, not to the extent of sphincter defect.

Introduction

Obstetric anal sphincter injury (OASIS) occurs in 0.5%-7.0% of vaginal deliveries [1]. In addition, occult defects have been documented in approximately 30% of multiparous women[2]. The reported prevalence of faecal incontinence (FI) following OASIS is between 15% and 61% [1, 3], with a twofold-increased risk of FI compared with the non-exposed [4]. However, the relation between the extent of sphincter defect and clinical symptoms is controversial, and sphincter disruption is only one factor in the complexity of FI [5].

Sacral neuromodulation (SNM) has the potential to modify the complex neuromuscular function required for defecation [6]. One advantage of SNM is the staged procedure in which patients with a successful percutaneous nerve evaluation (PNE) are selected for permanent implantation. Substantial improvement during PNE predicts a successful long-term outcome of SNM [7-9].

SNM is the preferred first line treatment for FI after failure of conservative treatment [5]. However, international guidelines are inconsistent regarding the role of SNM if the anal sphincter complex is disrupted [10, 11]. Although a sphincter defect is no longer considered a contraindication for SNM [10-14], both the European SNS Bowel Study Group [12] and a recent review [13] emphasize the poor quality of the few published studies and the need for prospective studies designed to investigate how the extent of the sphincter defects affects the outcome.

The purpose of this study was to assess efficacy during PNE using the tined lead and the Verify® neurostimulator and relate the outcomes to baseline factors with special emphasis on the extent of sphincter defect in women with FI following OASIS.

Materials and Methods

In this prospective study, 75 consecutive women with a history of OASIS and FI refractory to conservative treatment were assessed for eligibility from February 2012 to March 2014 at the tertiary referral colorectal unit at the University Hospital of North Norway. One woman declined to participate, and three were excluded by exclusion criteria (Table 1). Another eight women signed informed consent but postponed or declined treatment for various reasons. Sixty-three underwent a 3-week PNE period and had available data for analysis (Figure 1). In the same period, 14 men and 15 women with FI without a history of OASIS underwent PNE.

Baseline evaluations included interviews, questionnaires assessing pelvic floor dysfunction and quality of lfe (QoL) [15-18], a two-week bowel habit diary and 3D endoanal ultrasonography (EAUS) (Table 2). The extent of the sphincter defect was classified according to the EAUS defect score [19, 20] by an independent investigator (SN) who was blinded to patient data. Further anal physiological testing was not included in this study.

Outcome evaluation was based on reports from bowel habit diaries during the three-week PNE compared with baseline. The St. Mark's score and the other questionnaires [15-18] were only administered at baseline before PNE and were not administered during or at the end of the PNE period because those measurements are not designed or validated for measuring changes over short intervals such as a three-week PNE period [12, 15]. The primary outcome was efficacy, defined as the percentage reduction in weekly FI episodes during PNE compared with baseline. A successful test was defined as a 50% or greater reduction in FI episodes. A weekly FI episode was defined by leakage of loose or solid stool, not flatus incontinence. Urgency was defined

as inability to defer defecation for 15 minutes.

Written informed consent was obtained from all participants. The Regional Committees for Medical and Health Research Ethics, North Norway approved the protocol (number 2011/1300/REKnord).

Operative Procedure (PNE)

All procedures were performed by the same team, with one surgeon (MR), using a tined lead instead of a temporary lead. The tined lead (3093, Medtronic, Minneapolis, Minnesota, USA) was placed through the S3 or S4 foramina using a Seldinger technique and fluoroscopy with local anaesthetic in combination with monitored sedation. According to recommendations [21], the tined lead was positioned to achieve a low-threshold motor response on as many of the four electrodes as possible. The tined lead was connected to an external neurostimulator (Verify® model 3531, Medtronic) by an extension wire. Three programs eliciting a low-threshold sensory response, with best response defined as sensation nearest to the anus, were established in the operating room.

Because of long travel distances, patients came to hospital the day before surgery. They were invited to participate in group conversations with 6 to 8 patients with the opportunity to share experiences and questions. Patients were discharged after learning to adjust stimulation with the patient controller (Model 3537, Medtronic). Participants were offered sick leave for the entire 3-week PNE period and were followed by weekly phone calls. Instructions for readjustment, including change of amplitude, were repeated to patients who reported minor response or painful stimulation. The extension wire was cut at skin level by the general practitioner after three weeks, terminating the PNE. Cutting the extension wire at skin level after the PNE

period has departmental practise since 2008, when the tined lead was introduced as the standard PNE procedure. The tined lead was left in place for definitive implantation in patients who had a successful test, usually two to four weeks later. Adverse events were recorded including infection, pain and adverse changes in bowel or urinary function [22].

Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]) and differences were assessed by the nonparametric Wilcoxon signed rank test. Categorical data are presented as frequencies and percentages and compared using the chi-squared test or the two-tailed Fisher's exact test. Correlations were assessed with Pearson correlation coefficients (r). Linear regression models (dependent variable reduction in weekly FI episodes) and logistic regression models (dependent variable successful PNE) were used to assess the associations with baseline independent variables with special emphasis on the extent of sphincter defect. Significant variables from unadjusted regression models were included in multivariable regression models. Model assumptions were assessed by residual analyses. A two-sided P value <0.05 was considered statistically significant. All analyses were performed using the SPSS program, version 22.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Fifty-six (89%) of the 63 women were responders with a 50% or greater reduction in weekly FI episodes. Responders achieved a 94.5% reduction in weekly FI episodes, from median (IQR) 4.8 (2.0-11.0) to 0.5 (0-2.0, p<0.001). The overall reduction in weekly FI episodes during PNE was 88% (IQR 50-100%), from 4.5 (2.0-10.0) to 0.5 (0-2.0)

(p<0.001). Twenty-nine women (46 %) reported no FI episodes during PNE, and another six (10%) reported less than one per week. All but one non-responder reported urgency at baseline. Overall, the reduction in weekly urgency episodes was 82% (62-100 %), from 6.5 (4.0-12.5) to 1.0 (0-3.0, p<0.001). Urgency disappeared in 18 of the 56 responders (32%), and another six (11%) reported less than one urgency episode per week.

Baseline factors

Differences in demographic data and baseline characteristics between responders and non-responders are listed in Table 3. Of the responders, 41 (73%) were postmenopausal compared with two (29%) of the non-responders (p=0.03). The median body mass index (BMI) was 27 (24-31) in responders compared with 24 (22-25) in non-responders (p=0.007). All five patients without a reduction in FI episodes during PNE had a BMI of less than 25. A higher BMI correlated with a greater percentage of reduction in FI episodes (r= 0.34, p=0.007).

St. Mark's incontinence score and QoL

The severity of FI at baseline, graded by a St. Mark's score did not significantly correlate with efficacy (r=0.20, p=0.1). However, the baseline St. Mark's score was 18.0 (15.3-20.0) in responders compared with 15.0 (12.0-16.0) in non-responders (p=0.004). None of the four domains in the symptom specific QoL scale differed between responders and non-responders (Table 3). However, poorer reporting of the subscale coping at baseline indicated a greater reduction of FI episodes (r=-0.27, p=0.03). A similar tendency for

general QoL at baseline was observed, with poorer general QoL correlating with a greater reduction in FI episodes (r =-0.25, p=0.051).

EAUS assessment of the anal canal

In two responders, the distal sphincter was not included in the 3D EAUS data file and was thus impossible to score. Eight of the 63 women, six responders and two non-responders, had a secondary sphincter repair between 3 and 17 years prior to PNE (Table 3). Two women had no structural defects after primary repair and one woman following secondary repair; all three were responders. An isolated external anal sphincter (EAS) defect was identified in 46 patients, 41 responders (73 %) and five non-responders (71%) (p=0.8). A combined EAS and internal anal sphincter (IAS) defect was revealed in 12 women, 10 responders (18%) and 2 non-responders (29%, p=0.6). The median EAUS defect score did not differ between responders and non-responders with 2 (1-4) and 3 (IQR 1-4), respectively (p=0.4). The EAUS-defect score did not correlate with a reduction in FI episodes overall (r=-0.11, p=0.3,) or in premenopausal (n=20, r =0.2, p=0.4) or postmenopausal (n=43, r=0.02, p=0.9) women.

Urinary incontinence (UI)

UI was defined as concomitant when the validated ICIQ-UI SF score was higher than zero [17]. Concomitant UI was detected in 47 women (75%); seven (11%) with mild and 40 (63%) with moderate to severe UI. The ICIQ-UI SF score was 8 (3.3-15.8) in responders compared with 0 (0-9) in non-responders (p=0.07). Only one non-responder reported urge UI compared with 35 responders (p=0.036). Concomitant urge UI at baseline was also correlated with a reduction in FI episodes during PNE (r=0.45, p<0.001). Higher baseline ICIQ-UI SF scores were associated with a greater reduction in FI episodes during PNE (r=0.38, p=0.002).

Sexual function

Only half of the participants were sexually active: 26 (48%) responders and four (57%) non-responders (p=0.8). Twenty-two (35%) of the sexually active women reported other problems related to sexual activity, primarily fear of FI (n=19) during intercourse. Sexual function was not correlated with outcome (p=0.1), and there were no differences between responders and non-responders.

Operative procedure and adverse events

A total of 47 patients (75%) had the tined lead inserted in the S3 foramen and 16 in the S4 foramen, without differences between responders and non-responders (p=0.6). Motor response was revealed in all patients. The median sensory threshold amplitude was amplitude 1.0 (0.3-2.0); 1.0 (0.7-1.1) in responders compared with 0.8 (0.5-1.0) in non-responders (p=0.3). The pulse width was 210μs and frequency 14Hz.

Two responders (3%) had the tined lead removed after PNE because of infection with Staphylococcus Aureus. Another 14 (25%) reported pain at the electrode site or in the extremities, three non-responders (43%) and 11 responders (20%) (p=0.2). Pain during PNE was inversely correlated with a reduction in FI episodes during PNE (R=-0.29, p=0.02). Pain was related to low BMI; 8 of 22 (36%) with a BMI<25 reported pain compared with 6 of 41 (15%) with a BMI>25 (R=0.25, p=0.049).

Multivariable regression model

The St. Mark's score was the only variable significantly associated with successful PNE in the multivariable logistic regression model, with an odds ratio of 1.47 (95% CI 1.01-2.14, p=0.046) (Table 4).

Concomitant urge UI (p= 0.004) and BMI (p=0.03) were the two baseline factors significantly associated with the percentage reduction in weekly FI episodes in the multivariable linear regression model. Pain during PNE (p=0.046) was related to reduced efficacy in the same model (Table 5).

Discussion

This is one of the largest prospective series in which efficacy during PNE, using a tined lead and the Verify® external neurostimulator, was related to baseline factors in women with faecal incontinence following OASIS. The vast majority had successful outcomes; nine of ten were responders with a reduction in weekly FI episodes of more than 90%. The baseline St. Mark's score was the sole factor predicting PNE outcome in the multivariable logistic regression model. In the multivariable linear regression model, concomitant UI and a higher BMI were related to greater reduction in weekly FI episodes whereas pain during PNE was related to unfavourable outcome. The extent of the sphincter defect did not affect the outcome.

Our primary outcome was efficacy defined as the percent of reduction in weekly FI episodes recorded in the bowel habit diary. Patients with a reduction of 50% or greater were defined as responders. Scoring systems such as the St. Mark's score[15], Rockwood QoL[16] and ICIQ-UI SF[17] are preferred for tracking symptom load and QoL in long-term follow up. However, these questionnaires are not designed or validated for measuring changes over short intervals such as the three-week test period and consequently are not used to evaluate PNE outcomes [12, 23].

In this study, standardization of the PNE with positioning of the tined lead to achieve low motor and sensory thresholds on three to four poles resulted in a reduction in FI episodes of 90%, with nine of ten being responders. A 90% reduction of FI episodes during PNE, has been shown to be predictive of patient satisfaction with SNM [24] and with a lower probability of failure of SNM over the long term [7-9]. Low threshold stimulation is believed to improve the outcomes of both PNE and permanent SNM [25-27]. The new external neurostimulator (Verify®) may have contributed to the high success rate. This neurostimulator is more stable than the previous model and enables delivery of a more accurate amplitude similar to permanent stimulation.

Our PNE success rate is higher than the 66.8% success rate from the European SNS outcome study group [7] but similar to the results of a recent review including 119 women with FI and sphincter disruption [13]. However, 9 of 10 series in this review were retrospective. Furthermore, comparing outcomes from different studies is challenging because of variations in the definition of success, the surgical procedure for lead placement and the type of lead applied [28].

The baseline St. Mark's score was the sole factor predicting a successful PNE in the multivariable logistic regression model. Except for the importance of loose stool consistency [27], the severity of FI at baseline has not been related to PNE outcome [7, 8, 29, 30]. A greater improvement in postmenopausal women with more severe FI, as shown in our study, may be explained by the fact that these women have more to gain than younger patients with a more recent repair, a better recovery capacity and less co-morbidity. This idea is supported by a meta-analysis in which greater improvement after SNM was observed in postmenopausal women with severe FI [31]. Moreover,

given that sphincter injury is only one factor in the complexity of FI [5], a higher St. Mark's score may express more severe and complex damage to the pelvic floor. It is possible that SNM works better in severe FI because it has "the potential to modify all aspects of the coordinated neuromuscular functions required for defecation" [5, 6]. This possibility is supported by our finding that concomitant UI was correlated with a greater reduction in FI episodes during PNE.

Concomitant UI was related to a favourable outcome of PNE in our study. Three-quarters of women suffered from FI and concomitant UI. Previous studies have reported a prevalence of 30%- 50% [1, 32, 33]. The high prevalence of concomitant UI may be explained by the systematic assessment using a validated questionnaire with a low cut-off value defining UI. Traumatic vaginal delivery may also contribute to complex damage to the pelvic floor organs, resulting in concomitant UI, given the close relations among the organs [34]. Because SNM was originally developed for UI [35] and has the potential to modify afferent nerve activity for both urinary and bowel control rather than for the efferent motor activity and sphincter complex alone [6], it may be an appropriate treatment for women with FI and concomitant UI [33, 34, 36].

In the present study a higher BMI was associated with a greater reduction in weekly FI episodes during PNE. The literature is inconsistent regarding an assumed association between BMI and efficacy during PNE both for FI and UI, but increased rates of reoperations and complications have been described in SNM patients with lower BMI [37-41]. While series exploring predictors of SNM for FI have failed to show an association between BMI and outcome [8, 29, 30], a relation between low BMI and unfavourable outcome as shown in our study has also been demonstrated in urological

patients[37, 38, 41] and children [39]. Bilateral migration of tined leads in a thin patient is thoroughly discussed by Kessler et al in 2005 [41]. A possible mechanism may be that the lead is more prone to displacement with subsequent reduced efficacy in thinner patients who have less lean muscle and subcutaneous tissue to anchor the tined lead[41]. Variations in the lead position may even generate painful stimulation. If pain necessitates a reduction in amplitude, the efficacy can be reduced [42]. Pain in turn during PNE was related to unfavourable outcomes also in the current study.

In the current study, the extent of sphincter defect did not relate to outcome. Sphincter defects were classified according to the validated EAUS defect score [20]. The literature is conflicted regarding the importance of the extent of sphincter defect and PNE outcome. Some researchers observe no relation [8, 13] whereas others have suggested that an EAS defect increases the risk of PNE failure without excluding patients from SNM [30, 43]. Caution should be exercised when drawing conclusions from because the current data as few women had large defects. Nevertheless, these data support the conclusion that the presence of a sphincter defect does not preclude PNE and that SNM should be considered as first-line treatment for all women with FI following OASIS regardless of the extent of sphincter defect, in the absence of other indications for perineal reconstruction [5, 13, 31, 43, 44].

The strength of the present study is the homogeneous group based on aetiology, confined to women with FI following OASIS, which is the largest subgroup with FI [45]. Another strength is the standardization of the method including the tined lead. A limitation of this study is the limited number of non-responders.

Because standardization of the lead placement to achieve low motor and sensory

thresholds on three or four poles resulted in a high success-rate, the predictive value of the PNE using a tined lead and the staged procedure must be re-evaluated [46]. Under these circumstances, a one-stage implant to simplify the patient's flow and management may be possible, the benefits being reduced hospital stay and exposure to anaesthesia. Furthermore, less instrumentation could lead to a reduced risk of implant infection and patients could avoid the restrictions imposed by the external neurostimulator system. However, this paradigm requires assessment in a well-designed multicentre trial with a cost-benefit analysis.

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Table 1 Eligibility criteria

Inclusion criteria	**Exclusion criteria**
History of OASIS	Pregnancy
Faecal incontinence with St. Mark's score > 8 and weekly incontinence episodes	Immunosuppression
Failed **conservative treatment** (dietary modification or constipating medication, pelvic floor exercises with or without biofeedback, supportive devices such as pads, plugs, and trans anal irrigation)	Previous major pelvic surgery including irradiation to pelvic organs for cancer within the past five years
Informed consent	Untreated external rectal prolapse
18 years or older	Untreated perianal fistula
	Active Inflammatory Bowel Disease (IBD)

Table 2 Evaluation at baseline, during the three-week PNE and outcome measurement

Baseline	**Procedure**	**Outcome measurement PNE**
Demographic data: Age (years) Menopausal status Body mass index (BMI, kg/m^2) Obstetric history Previous surgical procedures 3D endoanal ultrasonography defect score [20]		
Questionnaires **St. Mark's incontinence score** [15] Faecal incontinence QoL score (Rockwood)[16] EQ-5D™ (EuroQol Group, Rotterdam, the Netherlands) UI (ICIQ-UI SF) [17] Sexual function [18]		
2-week bowel habit diary: Weekly FI episodes Weekly urgency episodes Weekly bowel-emptying episodes		**3-week bowel habit diary:** **Reduction in weekly FI episodes** Reduction in weekly urgency episodes Reduction in weekly bowel-emptying episodes
	Sensory threshold (amplitude, milliampere mA) Foramen (level) Adverse event (pain, infection)	

Table 3. Demographic data and baseline characteristics of responders (≥50% reduction in faecal incontinence episodes) compared with non-responders (<50% improvement in faecal incontinence episodes). Values are expressed as either numbers (percent) or median (interquartile range).

	Responders (n=56)	**Non-responders (n=7)**	**P-value**
Age, years	61 (50-67)	43 (41-67)	0.2
Menopausal status			**0.03**
Premenopausal	15 (27%)	5 (71%)	
Postmenopausal	41 (73%)	2 (29%)	
Body mass index, kg/m²	27 (24-31)	24 (22-25)	**0.007**
Obstetric history			
Vaginal deliveries	2.0 (2-3)	2.0 (1-2)	0.09
Instrumentation	16 (29%)	1 (14%)	0.7
Degree of OASIS			0.4
3rd degree tear	21 (38 %)	4 (57%)	
4th degree tear	35 (62%)	3 (43 %)	
EAUS defect score (0-7)	2.0 (1-4)	3.0 (1-4)	0.4
Previous secondary sphincter repair	6	2	0.2
Previous anorectal surgery	14 (25%)	3 (43%)	0.09
Previous gynaecological surgery including for urinary incontinence	23 (41%)	2 (29%)	0.1
St. Mark's score (0-24)	18.0 (15.3-20.0)	15.0 (12-16)	**0.004**
Duration of FI			0.4
1-10 years	30 (54%)	5 (71%)	
More than 10 years	26 (46%)	2 (29%)	
Rockwood quality of life score			
Lifestyle (0-4)	2.6 (1.9-3.2)	3.0 (2.1-3.6)	0.3
Coping/behaviour (0-4)	1.6 (1.2-2.1)	1.9 (1.6-2.4)	0.1
Depression (0-4)	3.0 (2.1-3.8)	3.2 (2.4-3.6)	0.6
Embarrassment (0-4)	1.7 (1.3-2.0)	2.3 (1.3-2.7)	0.3
EQ-5D™			
General health (VAS scale 0-100)	63 (50-78)	90 (54-90)	0.1
Urinary Incontinence	44 (79%)	3 (43%)	0.06
Urge urinary Incontinence	36 (97%)	1 (14%)	**0.04**
ICIQ-UI SF score (0-21)	8 (3.3-15.8)	0 (0-9)	0.07

OASIS=obstetric anal sphincter injury. EAUS=endoanal ultrasonography. EQ-5D=European Quality of Life-5 Dimensions. ICIQ-UI SF= International Consultation on Incontinence Questionnaire- Urinary Incontinence Short Form.

Table 4. Multivariable analysis of predictors of successful PNE defined as 50% or more reduction in weekly faecal incontinence episodes.

	Univariable regression model (Crude)			Multivariable regression model (adjusted*)		
	OR	95% CI	P-value	OR	95% CI	P-value
Menopausal status	6.83	1.20-39.1	**0.031**	3.32	0.37-30.1	0.29
Body mass index (kg/m^2)	1.37	1.03-1.81	**0.029**	1.48	0.91-2.43	0.12
St. Mark's score (0-24)	1.51	1.11-2.05	**0.009**	1.47	1.01-2.14	**0.046**
Urge UI	10.0	1.13-88.9	**0.039**	4.62	0.38-55.7	0.23

*Mutually adjusted for variables significant from univariable model. OR=Odds ratio, CI= Confidence interval

Table 5. Linear regression analysis for the association between efficacy (defined as percent reduction in weekly faecal incontinence episodes) and clinical characteristics.

	Univariable regression model (Crude)			Multivariable regression model (adjusted*)		
	Beta	95% CI	P-value	Beta	95% CI	P-value
Urge UI	26.5	12.9-40.2	**<0.001**	20.0	6.6- 33.5	**0.004**
Body mass index (kg/m^2)	2.1	0.6-3.6	**0.007**	1.5	0.1-2.9	**0.03**
FIQL Coping (0-4)	-14.3	-27.5 to -1.1	**0.03**	-3.8	-17.6-10.0	0.6
Eq-5D VAS (0-100)	-0.4	-0.7- 0.001	*0.051*	-0.2	-0.6-0.2	0.3
Pain	-20.9	-38.2- 3.5	0.02	-15.6	-31.5-0.4	**0.046**

*Mutually adjusted for the listed variables. Beta=Linear regression coefficients, CI=Confidence interval

Figure 1. Flow chart of enrolment in the study