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Sacral neuromodulation compared with injection of bulking agents for faecal incontinence following obstetric anal sphincter injury – A randomised controlled trial

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MR: Conception and design of the work; acquisition, analysis and interpretation of data; writing of the manuscript

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Abstract presentation at ICS (International continence society annual meeting) Montreal, Canada, 09.10.15; 8 min, the abstract is attached.

Results were also presented at the Artic Pelvic floor Meeting in Tromsø, Norway, 13. 11.15.

Registration number:

The Regional Committee for Medical Research Ethics, North Norway (REK NORD 2011/1300) approved the trial. The trial was registered at ClinicalTrials.gov with number NCT01528995.

Keywords:

Faecal incontinence

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Obstetric anal sphincter injury

Sacral neuromodulation

Bulking agents

ABSTRACT

Aim:

The purpose of this trial was to compare the effectiveness of sacral neuromodulation (SNM) with a sub-mucosal injection of collagen (Permacol®) in women with faecal incontinence following obstetric anal sphincter injury (OASIS).

Method:

This single blinded randomized controlled trial at two hospital units in Norway included women with faecal incontinence following OASIS. Eligible women who had had a successful percutaneous nerve evaluation were randomly assigned to SNM or Permacol®. The primary

outcome was the difference in the St. Mark's incontinence score between baseline and 6 months. Secondary outcomes were changes in the disease-specific quality of life (FIQL) and urinary incontinence (ICIQ-UI-SF) scores.

Results:

Fifty-eight women were randomly assigned to SNM (n=30) and Permacol® (n=28). The reduction in the St. Mark's score between baseline and 6 months was 11.2 (SD 5.3) in the SNM group versus 2.3 (SD 5.0) in the Permacol® group, resulting in a difference of 8.9 (95% CI 6.1-11.7, p<0.0001).The differences in the four scales of FIQL (lifestyle, coping, depression, embarrassment) were 0.90 (95% 0.50-1.30, p<0.001), 1.05 (0.62-1.47, p<0.001), 0.52 (95% CI 0.16-0.87, p=0.005) and 0.95 (95% CI 0.50-1.40, p<0.001), respectively in favour of SNM. The difference in the ICIQ-UI-SF was 5.0 (95% CI 1.97-8.02, p=0.002) in favour of SNM. There were 9 minor adverse events in the SNM group compared to seven in the Permacol® group (p=0.77).

Conclusion

SNM was superior to Permacol® in terms of reduction of St Mark's score, ICIQ-UI-SF and the change of the FIQL in women with faecal incontinence following OASIS.

Registration no.:

The Regional Committee for Medical Research Ethics, North Norway (REK NORD 2011/1300) approved the trial. The trial was registered at ClinicalTrials.gov with number NCT01528995.

What does this paper add to the literature?

This is one of few randomized trials comparing two treatments that bridge the gap between conservative management and reconstructive surgery for women with faecal incontinence following obstetric sphincter injuries. Sacral neuromodulation was found to be superior to Permacol® in all respects.

INTRODUCTION

Faecal incontinence and concomitant pelvic floor dysfunction following obstetric anal sphincter injuries are neglected health problems with a major impact on the quality of life. Affected women suffer from physical, psychological and social disabilities[1-3]. The prevalence and severity of faecal incontinence (FI) following obstetric anal sphincter injuries (OASIS) increases with age and is estimated to be 15-61%[1, 2]. Coexisting urinary incontinence (UI) is reported in more than 40% and sexual dysfunction ~~is impaired~~ in more than 30% of those with FI[1, 4, 5].

Management of FI following OASIS remains challenging. Sacral neuromodulation (SNM) bridges the gap between conservative treatment and reconstructive surgery which has more complications and long-term failure rates[6, 7]. The relationship between the extent of the sphincter defect and clinical symptoms is unclear, and the disrupted sphincter is only one factor in the complexity of FI and concomitant pelvic floor dysfunction[8]. International guidelines for the treatment of anal sphincter complex disruption are inconsistent regarding the role of SNM[9, 10].

Injection of bulking agents is another relatively minimally invasive treatment for FI that has been shown to improve the clinical outcome in several series and randomized trials[11-14]. The indication for bulking agents has expanded from passive FI with an intact sphincter complex to include women with urge FI and some degree of sphincter defect [14, 15]. Bulking agents have also been shown to be cost-effective compared with SNM and an attractive alternative to SNM[16], as treatment can be given as an outpatient with less equipment costs. However, SNM and injection of bulking agents

have not been compared in a randomized controlled trial, and uncertainty persists about the optimal choice of treatment for postobstetrical FI. The aim of this study was to compare the short-term effectiveness of SNM to sub-mucosal injection with collagen (Permacol®) in women with FI following OASIS.

METHOD

The study was designed as a single blinded, parallel, randomized controlled trial. Women with FI and a history of OASIS were enrolled from two tertiary colorectal units in Norway. Inclusion criteria were as follows: 1) FI defined as a St Mark's incontinence score[17] greater than 8 and 2) weekly episodes of passive and/or urge FI despite optimal conservative management (Table 1). All women had third- or fourth-degree perineal tears during childbirth diagnosed clinically [18]. The extent of sphincter defect at the time of inclusion was classified according to the endoanal ultrasonographic (EAUS) defect score [19, 20] by an expert (SN) who was blinded to the patient information.

According to the study protocol, all eligible women were offered a three-week percutaneous nerve evaluation (PNE) prior to randomization.. A successful PNE was defined as a 50% or greater reduction of FI episodes[9, 10]. This was a prerequisite for inclusion because implantation of SNM with a definitive pulse generator (IPG) requires a successful PNE[10]. The 50% chance of assignment to the Permacol® group despite successful PNE and the 6-month delay before SNM implantation even if Permacol® was ineffective were thoroughly discussed with the patients before obtaining written informed consent. The Regional Committee for Medical Research Ethics, North Norway

(REK NORD 2011/1300) approved the trial. The trial was registered at ClinicalTrials.gov with number NCT01528995.

Randomization

Patients were randomly assigned to receive either SNM or Permacol® with an equal allocation ratio (1:1), with randomly permuted block sizes of varying length (6 and 4) to conceal the allocation. Patients were stratified according to the recruitment centre.

Allocation was performed by a computer-generated, real-time, web-based randomization system (www.ntnu.no/dmf/akf/randomisering) that generated random allocation sequences. Until the study was closed these were known only by the administrators responsible for developing the randomization system. Assignment to intervention was implemented by local investigators (MR, AR).

Procedures

The PNE was performed under local anaesthesia along with with monitored sedation. The tined lead (3093, Medtronic, Minneapolis, MN, USA) was placed through the sacral foramina of S3 or S4 using the Seldinger technique and fluoroscopy as previously described[21]. For women assigned to SNM, the tined lead was subsequently connected to an internal pulse generator (IPG, Interstim II 3058 Medtronic, Minneapolis, MN, USA) placed in a subcutaneous pocket under local anaesthesia, using antibiotic prophylaxis both locally (CollatampG®) and intravenously (Cefuroxim). The IPG was programmed to elicit a low-threshold perianal sensory response. All of the patients received a patient programmer (ICon® 3037, Medtronic, Minneapolis, MN, USA) allowing adjustments or being able to turn the stimulation on and off. The IPG was reset at the three-month follow-up appointment, if there were adverse events, adverse sensation or

persisting weekly FI episodes. A specialist nurse was available to answer questions by telephone between the prescheduled follow-up appointments.

Cross-linked porcine dermal collagen (Permacol®, Tissue Science Laboratories, Aldershot, Hampshire, UK) was chosen because it is thought to be incorporated well into tissue, creating long lasting bulk in the submucosa[12]. In the lithotomy position, 1.5 mL Permacol® was injected via a proctoscope without anaesthesia or bowel preparation into the submucosa just above the dentate line in each of the four quadrants of the anal canal[11, 12, 15]. Antibiotic prophylaxis (Ciprofloxacin 500 mg x2) was given orally 30 minutes before the procedure. In the absence of adverse events, the procedure was repeated after three months if there were still weekly episodes of FI . For women allocated to Permacol®, the tined lead was removed at the six month follow-up appointment unless IPG was to be considered. Delayed implantation of the IPG was offered when there was an inadequate response to Permacol® at six months.

Outcome and blinding

The primary outcome measure was the difference in the reduction of the St. Mark's score between baseline and six months[17]. Secondary outcomes included differences in the change of disease-specific quality of life (FIQL) and generic quality of life (Euroqual, EQ-5D™) [22, 23], self-reported outcome assessment (satisfied/not satisfied), reduction of weekly FI episodes recorded from a bowel habit diary, UI and sexual function[24]. UI was defined as occurring concomitantly if the ICIQ-UI-SF score was higher than 0[25]. Sexual function was assessed by a translated, non-validated questionnaire designed for women with OASIS, developed by an expert group[24]. In

addition to any specific sexual problems, the term "bothersome sexual problem" was included in this questionnaire to avoid an over-diagnosis of sexual complaints [24].

Baseline data were obtained prior to PNE. Outcome assessments of St Mark's score and ICIQ-UI-SF and sexual function were performed by telephone interview prior to the 6-month follow-up appointment by a trained nurse who was blinded to treatment allocation throughout the study period. The patients were instructed by an information letter not to reveal the treatment arm. They were also sent a two-week bowel diary and the QoL questionnaires to complete themselves.

Sample size calculation

The sample size was calculated based on the assumption that a difference greater than 4 points in the reduction of the St. Mark's score between baseline and 6 months (primary outcome) between the groups was clinically relevant. Detecting this difference with a statistical power of 0.80 and a significance level of 0.05 with a two-sided test and assuming a standard deviation of 5.0 would require 25 patients in each group. Accounting for a dropout rate of 10%, assignment of 28 participants in each group was considered adequate.

Statistical consideration

Data were presented as the mean with standard deviation (SD) and median with interquartile range (IQR). Outcome variables were analysed using a linear regression, unadjusted and adjusted for the baseline symptom scores as covariates (ANCOVA)

according to recommendation. ANCOVA was pre-specified as the primary analysis in the study protocol [26, 27]. The effect sizes are presented as the mean with 95% confidence interval (CI) and a two-sided significance level of 0.05. Model assumptions were assessed by residual analyses. Non-parametric tests were used when assumptions were not met. Binary variables were presented as the number and percentage. Sexual function was presented as a descriptive analysis without statistical testing. The reason for this was a marked imbalance between the groups regarding sexual activity making statistical analysis unreliable. Correlations between the extent of sphincter defect and effectiveness were assessed with Pearson's correlation coefficient (r) (-1-1). The CONSORT guidelines (Consolidated Standards of Reporting Trials 2010)[28] were followed to ensure high quality of reported results. Statistical analyses were performed using the SPSS program, version 23.0 (SPSS Inc., Chicago, IL).

Additional analysis

We recognized that the study design might have introduced a bias in favour of SNM because a successful PNE was an inclusion criterion. To overcome this inherent selection bias, as recommended[7], a worst-case scenario for SNM and best-case scenario for Permacol® was created as follows: Of the seven women with unsuccessful PNE who were excluded, four were allocated to the Permacol® group. Each patient was given the best reduction in St Mark's score obtained after Permacol® injections. The other three were allocated to the SNM group, each given a reduction of zero in St Mark's score (worst possible). In this way, the best possible outcome after Permacol® injection could be compared with the worst possible outcome after SNM. The primary outcome

was then analysed. Because of imbalanced recruitment between the two centres, an additional sensitivity analysis excluding the two patients from St Olav's Hospital was performed.

RESULTS

Between March 2012 and March 2014, 77 consecutive women were assessed for eligibility. Fifty-six women from the University Hospital of North Norway and two from St Olav's Hospital were randomly assigned to SNM (n=30) or Permacol® (n=28) following a successful PNE. Two patients withdrew consent before entering treatment in the Permacol® group. Except for these two, all patients were available for analysis at six months (Figure 1). The trial was closed in September 2014 after reaching the sample size goal and completing all 6-month follow-up examinations.

The median age was 61 (IQR 50-67) years. A median of 39 years had passed since the obstetric injury (IQR 25.5-44). Because the women were referred from hospitals throughout Norway, information regarding the injury and primary repair was incomplete. Six women underwent secondary sphincter repair between 3 and 17 years prior to enrolment.

The median St Mark's score was 18.0 (IQR 15.8-20.0). Two (3%) women reported isolated passive FI, 13 (23%) reported mixed FI and 43 women (74%) described urge FI. Demographics and baseline characteristics were similar between groups except for some imbalance in concomitant pelvic floor dysfunction (Table 2).

Extent of sphincter defects

The EAUS defect score was unavailable in four patients assigned to SNM: In two patients the distal sphincter was not included in the EAUS-file, and files were missing in the two patients from St Olav's Hospital. Two women (4%) had no structural defects after the primary repair, and one woman had no defect (2%) following the secondary repair. An isolated external anal sphincter (EAS) defect was identified in 40 patients (74%), and combined EAS and internal anal sphincter (IAS) defects were revealed in 11 patients (20%).

Faecal incontinence

The reduction in the St. Mark's score between baseline and 6 months was 11.2 (SD 5.3) in the SNM group versus 2.3 (SD 5.0) in the Permacol® group, resulting in a treatment difference of 8.9 (95% CI 6.1-11.7, $p<0.0001$) in favour of SNM (Table 3).

There was a weak correlation between the EAUS defect score and the baseline St Mark's score ($r=-0.19$). There was no correlation between the EAUS defect score and reduction of St. Mark's score in the SNM group ($r=0.001$), but the EAUS defect score had a moderate correlation with the Permacol®-group ($r=0.38$).

Twenty-eight patients (93%) had a 50% or greater reduction in weekly FI episodes after SNM compared to nine patients (32%) following Permacol® application ($p=0.001$). Seventeen patients (57%) described no weekly FI episodes 6 months after SNM compared to three patients (11%) after Permacol® ($p<0.001$). No weekly urgency episodes were described in 18/29 (62%) women after SNM compared to 6/25 (24%) women following Permacol® ($p= 0.007$) (Table 3).

Quality of life (QoL)

SNM was superior to Permacol® regarding the four domains of the FIQL, including lifestyle (0.90, 95% CI 0.50-1.30, p<0.001), coping (1.05, 95% CI 0.62-1.47, p<0.001), depression (0.52, 95% CI 0.16-0.87, p=0.005) and embarrassment (0.95, 95% CI 0.50-1.40, p<0.001) (Table 3).

Women with SNM achieved an improvement in their EQ-5D™ global health score (0-100) of 11.1 (SD 21.9) compared to 2.7 (SD17.8) in women treated with Permacol®, but the difference (8.4, 95% CI -2.4-19.3) was not significant (p=0.12). The difference in the EQ-5D index (0.031, 95% CI -0.14-0.07; p=0.55) was also not significant (Table 3).

Overall, 23 (77%) women in the SNM group were satisfied with their treatment after 6 months compared to only 3 (11%) satisfied women in the Permacol® group (p<0.001).

Urinary incontinence

Concomitant UI was reported by 43 (74%) women—27 (90%) in the SNM group and 16 (61%) in the Permacol® group. The women receiving SNM achieved a mean reduction in the ICIQ-UI-SF score of 5.3 (SD 5.8) compared with a reduction of 0.27 (SD 5.4) in women treated with Permacol®. The difference in the reduction of the ICIQ-UI-SF score was 5.0 (95% CI 1.97-8.02 p=0.002) in favour of SNM at six months; when adjusting for the baseline ICIQ-UI-SF score, the difference was 3.0 (0.2-5.9) (Table 3).

Sexual function

There was some imbalance in baseline sexual activity, as there were 19 (63%) sexually active women in the SNM group and 8 sexually active women (29%) in the Permacol® group. After 6 months the number of sexually active women was 16 in the SNM group and 6 in the Permacol® group (NS). A sexual complaint among the sexually active women was reported in 14/19 (74%) in the SNM group and 7/8 (88%) in the Permacol® group at baseline. After six months, 5/16 (31%) in the SNM group and 5/6 (83%) in the Permacol® group had a sexual complaint. The number of women reporting bothersome sexual problems from baseline to 6 months changed from 11/19 (58%) to 4/16 (25%) in the SNM group and from 6/8 (75%) to 5/6 (83%) in the Permacol® group.

Adverse events

Adverse events were minor, without significant differences between the groups (p=0.77). No infections were detected in either of the groups. After SNM, nine patients (35%) reported adverse events at six months: One patient reported pain related to the IPG and one described pain in her leg Five women reported a deterioration of urinary function, which resolved after resetting the IPG. Two women were referred to specialists for further investigation after 6 months because of deterioration of urinary incontinence. The IPG was reset during follow-up in 17 (57%) patients, including an adjustment of the amplitude from 1.05 (SD 0.48) mA to 1.41 (SD 0.85) mA and readjustment because of pain (n=1) or deterioration of urinary function (n=7).

Two (8%) women did not receive a second injection with Permacol® because of anal pain after the first injection, and another woman refused because of lack of effectiveness. Five (19%) reported mild symptoms of obstructed defecation that did not require treatment.

Additional analysis

In the worst-case scenario, seven women representing those excluded after unsuccessful PNE were added to the analysis of the primary outcome: The reduction of St Mark's score was set to 0 in three women added to the SNM-group (worst possible response) and 16 in four patients added to the Permacol®-group (best response achieved after Permacol® injection). In the worst-case scenario for SNM, the estimated reduction of St Mark's score was 10.1 (95% CI 7.9-12.3) compared to 4.1 (95% CI 1.7-6.6) in the best-case scenario for Permacol®. The difference of 6.0 (95% CI 2.7-9.3) was unaffected by the adjustments and remained highly significant in favour of SNM ($p=0.001$). The sensitivity analysis, excluding the two patients from St Olav's Hospital, did not affect the outcome with a difference in the effectiveness of 8.8 (95% CI 6.03-11.6) $p<0.001$.

DISCUSSION

This is the first randomized controlled trial to compare the effectiveness of SNM and perianal bulking injections for the treatment of FI following OASIS. SNM was superior to Permacol® at six months compared with baseline in the reduction of the St Mark's score and ICIQ-UI-SF score, changing of FIQL score and improvement of patient satisfaction.

This trial was designed in 2011 to establish the role of Permacol® and SNM in the treatment algorithm of FI following OASIS, regardless of type of incontinence and extent of sphincter defect. Although the effectiveness of both SNM and bulking agents in women with FI following OASIS was uncertain, the use of bulking agents became widespread due to their simplicity and suggested cost-effectiveness compared with SNM [16]. Consequently, a comparison between the two treatments was warranted [6, 29-32]. Permacol® was selected in this trial because the efficacy of an alternative compound in which the dextranomer in stabilized hyaluronic acid (NASHA Dx) was disappointing with no differences compared to traditional biofeedback [15]. Symptom scores and the quality of life were also unchanged in a multicentre randomized trial comparing NASHA Dx with placebo [11]. On the other hand, Permacol® was believed to resist breakdown by collagenase, thereby maintaining its long-standing bulk in the submucosa[12].

Our primary outcome (reduction of the St Mark's score) has been shown to correlate with QoL in our study, similar to others[33] and clearly supports the difference in effectiveness between the two treatments in favour of SNM. The effectiveness of SNM was similar to findings from several published case series and some randomized trials with regard to reducing symptom scores by 8 to 13 points, reducing the number of weekly incontinence episodes, achieving complete continence in more than a third of patients, improving the ability to defer defecation (if evaluated) and all categories of FIQL score when assessed, and achieving efficacy unrelated to extent of sphincter defect [7, 8, 34]. The effectiveness of Permacol® in this study was rather disappointing compared with three series showing success rates of 53%, 56% and 72% [12-14], but

similar to a pilot trial comparing perianal injection of 15 ml Permacol® and Bulkamid®[35]. Disease-specific QoL was only assessed in one paper, which reported minor changes similar to those observed in this trial [12]. Two of the retrospective series included patients with EAS defects in addition to those with IAS defects without demonstrating a correlation between sphincter morphology and outcome [13, 14].

Although there is no clear definition of a successful and clinically relevant outcome of treatment for FI[36], a St Mark's score below 9 after treatment is assumed to be clinically significant and associated with improved QoL[37]. In the present study, this outcome was achieved after SNM but was not after Permacol® injection. Our observation that patients who experienced corresponding improvements of their FIQL scores after SNM compared to patients who experienced no improvement following Permacol® was consistent with a recent Cochrane review where the clinical relevance of bulking agents was questioned [38]. The lack of clinical improvement of Permacol® in women with FI following OASIS was further supported by the fact that only 11% of the women were satisfied with Permacol® after 6 months compared with approximately three-quarters of satisfied women in the SNM group. This lack of effectiveness suggests that Permacol® has no place in the treatment for FI following OASIS despite its simplicity, minimal invasiveness and low cost as recently stated in an editorial[39].

Concomitant UI was reported by three-quarters of the women. We did not expect Permacol® to improve concomitant UI as it acts locally in the anal canal[38]. SNM enhances continence by neuromodulation of different levels of the nervous system[40].

SNM has the potential to modify afferent nerve activity for both urinary and bowel control and originally was developed for UI, so some improvement of concomitant UI was predictable [40, 41]. The trial was not powered to detect differences in improvement in subgroups, but our findings support SNM as the treatment of choice for double incontinence (FI and UI)[42, 43]. Change in sexual function following SNM has been reported previously[44].

At least three different randomized controlled trials have shown that one-third of the patients with FI who received sham-treatment reported an improvement with 50% reduction of FI episodes[11, 45, 46], and an identical reduction in the incontinence score in the sham and the active treatment group[11]. The placebo effect observed in sham-treatment of FI in general should therefore not be neglected[38]. It is possible that the effectiveness of Permacol® observed in one-third of our patients is due to a placebo effect.

The strength of this trial is the randomized design and blinding of the outcome assessments. The study was restricted to women with FI following OASIS, representing the main subgroup of patients with FI[6]. Additionally, UI and sexual dysfunction were assessed as a part of the multidisciplinary approach to pelvic floor disorders at our hospital. A limitation of this study is the inherent selection bias related to the exclusion of all patients with unsuccessful PNE prior to randomization. This potential bias was compensated for by creating a worst-case scenario and including it in the analysis. This did not affect the highly significant effectiveness of SNM compared with Permacol®. Another limitation was related to imbalanced recruitment between the two centres,

making the results less generalizable. However, additional sensitivity analysis did not affect the outcomes either.

In conclusion, SNM was superior to Permacol® for nearly all outcome measures and should be the preferred treatment for women with weekly FI episodes following OASIS. These results indicate that Permacol® has no place in the algorithm and treatment for substantial FI following OASIS.

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Table 1. Eligibility criteria

Inclusion criteria	**Exclusion criteria**
Preceding successful percutaneous nerve evaluation (PNE), defined as 50 % or greater reduction of weekly episodes of faecal incontinence during PNE	Unsuccessful percutaneous nerve evaluation (PNE), defined as less than 50 % reduction of weekly faecal incontinence episodes during PNE
History of obstetric anal sphincter injury (OASIS) ~~confirmed by EAUS~~	Pregnancy
St Mark's score > 8 and weekly episodes of passive and/or urge faecal incontinence	Immunosuppression
Refractory to at least 6 months of tailored conservative treatment, such as supportive devices, including paddings and plugs; dietary modification; constipating medication; pelvic floor exercises with or without biofeedback; and transanal 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)
	Previous injection of an anal bulking agent
	Previous lateral sphincterotomy

Table 2 Baseline characteristics of all assigned patients (n=58).

	SNM (n=30)	Permacol® (n=28)
Age, years		
Mean (SD)	*58.5 (12.6)*	*56.8 (11.1)*
Median (IQR)	*62.5 (51.3-68)*	*58.0 (50.0-66.0)*
BMI, kg/m^2		
Mean (SD)	*28.5 (4.8)*	*26.5 (4.6)*
Median (IQR)	*28.4 (25.3-30.8)*	*26.0 (22.1-29.6)*
Menopausal status		
Premenopausal	*8 (73%)*	*7 (25%)*
Postmenopausal	*22 (27%)*	*21 (75%)*
Vaginal deliveries		
Mean (SD)	*2.7 (1.4)*	*2.5 (0.8)*
Median (IQR)	*2.5 (2.0- 3.3)*	*2.0 (2.0-3.0)*
Faecal Incontinence		
Type of faecal incontinence		
Passive	*1 (3%)*	*1 (4%)*
Mixed	*7 (23%)*	*6 (21%)*
Urgency	*22 (74%)*	*21(75%)*
Duration of Symptoms		
1-5 years	*6 (20 %)*	*3 (11%)*
6-10 years	***17 (56 %)***	***5 (18%)***
> 10 years	***7 (24%)***	***20 (71%)***

Bowel diary data		
Weekly FI episodes		
Mean (SD)	*10.1 (11.1)*	*5.2 (5.0)*
Median (IQR)	*6.3 (2.0-12.8)*	*3.5 (1.6-7.5)*
Weekly urgency episodes		
Mean (SD)	*11.3 (7.9)*	*7.4 (5.1)*
Median (IQR)	*10.0 (5.9-14.6)*	*6.0 (3.6-11.1)*
Days with FI per week		
Mean (SD)	*3.9 (2.0)*	*3.1 (2.2)*
Median (IQR)	*4.0 (2.0-6.0)*	*2.3 (1.1-4.8)*
Grade of the obstetric anal sphincter injury		
Third degree	*4 (13%)*	*3 (11%)*
Fourth degree	*19 (63%)*	*16 (57%)*
Unknown	*7 (23%)*	*9 (32%)*
EAUS defect score (0-7) (n=54)	*26*/30*	*28*
Mean (SD)	*2.1 (1.3)*	*3.0 (2.1)*
Median (IQR)	*2.0 (1.0-3.0)*	*3.0 (1.0-4.0)*
No detectable defect	*2/26 (8%)*	*1 (4%)*
Isolated EAS defect	*20/26 (77%)*	*20 (71%)*
Combined EAS+ IAS defect	*4/26 (15%)*	*7 (25 %)*
Secondary sphincter repair	*4 (13%)*	*2 (8%)*
Urinary incontinence **		
Urinary incontinence	*27 (90%)*	*18 (64%)*
Stress urinary incontinence	*2/27 (7%)* *2/30 (7%)*	*3/18 (17%)* *3/28 (11%)*
Urge urinary incontinence	*21/27 (78%)* *21/30 (70%)*	*14/18 (78%)* *14/28 (50%)*

TVT (yes)	*11 (21%)*	*6 (37%)*
Sexual function		
Sexual activity (yes)	*19 (63%)*	*8 (29%)*
***Pain (yes)	*6/19 (32%)*	*3/8 (38%)*
***Other problems (yes) 21	*14/19 (74%)*	*7/8 (88%)*
***Bothering problems	*11/19 (58%)*	*6/8 (75%)*

*Values are number (%), mean (SD), or median (interquartile range, IQR) for all women assigned to treatment. EAUS= endoanal ultrasonography. EAUS defect score ranged from 0 (no defect) to 7 (complete defect of both EAS= external anal sphincter and IAS= internal anal sphincter). * Two defects were impossible to classify, and 3D endoanal ultrasound was not available for two patients from St Olav's Hospital. **Urinary incontinence was defined as ICIQ-UI-SF score of 1 or more. ICIQ-UI-SF= International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form. It ranged from 0 (continent) to 21 (complete incontinence). TVT=tension-free vaginal tape surgery for urinary incontinence. ***Only assessed in sexually active.*

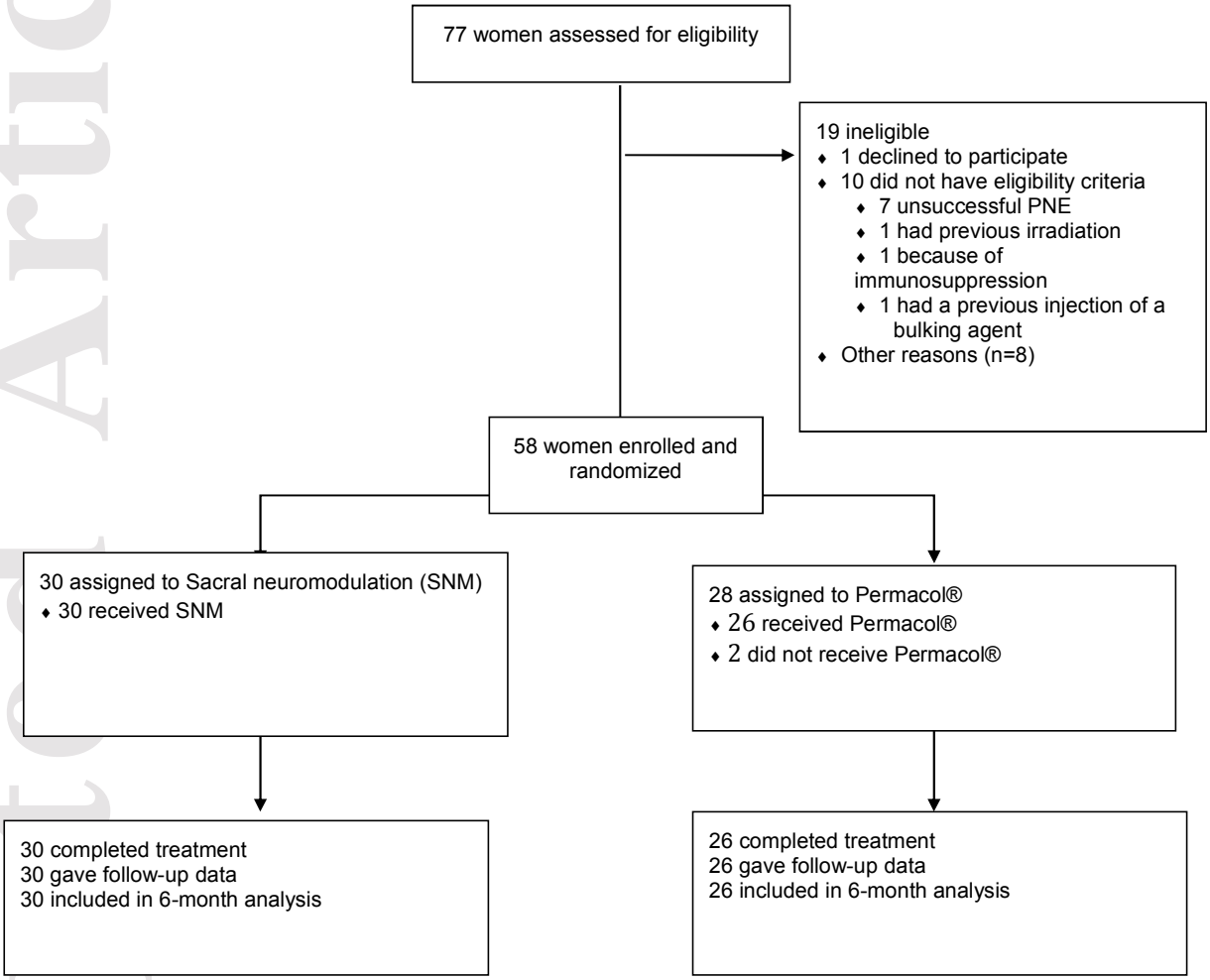
Table 3 *Differences between the SNM group (n=30) and Permacol® group (n=26) regarding the changes in the primary and secondary outcomes from baseline to 6 months*

Group	*Baseline*	*6 months*	*Change from baseline to 6 months*	*Difference in change from baseline to 6 months between the groups*			
				B, Unadjusted	***P-value***	*B, adjusted*[*]	***P-value***
Faecal incontinence							
St Mark's incontinence score (0-24)							
SNM	*19.0 (2.5)*	*7.7 (5.5)*	*11.2 (5.3)*	*8.93 (6.14-11.7)*	*<0.001*	*7.52 (4.67-10.4)*	*<0.001*
Permacol®	*16.8 (3.4)*	*14.3 (4.5)*	*2.3 (5.0)*				
Faecal incontinence quality of life scale (FIQL)							
Lifestyle (0-4)							
SNM	*2.40 (0.72)*	*3.45 (0.62)*	*1.05 (0.84)*	*0.90 (0.50-1.30)*	***<0.001***	*0.76 (0.41-1.10)*	***<0.001***
Permacol®	*2.63 (0.85)*	*2.83 (0.83)*	*0.15 (0.61)*				
Coping (0-4)							
SNM	*1.54 (0.48)*	*2.79(0.79)*	*1.25 (0.84),*	*1.05 (0.62-1.47)*	***<0.001***	*0.94 (0.53-1.34)*	***<0.001***
Permacol®	*1.76 (0.59)*	*1.9 (0.73)*	*0.20 (0.72)*				
Depression (0-4)							
SNM	*2.86 (0.87)*	*3.51(0.69)*	*0.65 (0.66)*	*0.52 (0.16-0.87)*	***0.005***	*0.53 (0.18-0.53)*	***0.001***
Permacol®	*2.83 (0.95)*	*2.97 (0.94)*	*0.14 (0.64)*				

Embarrassment (0-4)							
SNM	*1.72 (0.64)*	*3.03(0.78)*	*1.28 (0.84)*	*0.95*	***<0.001***	*0.94*	***<0.001***
Permacol®	*1.80 (0.55)*	*2.14(0.86)*	*0.36 (0.77)*	*(0.50-1.40)*		*(0.49-1.38)*	
EQ-5D							
EQ-5D VAS scale (0-100)							
SNM	*57.7 (19.5)*	*68.8(18.5)*	*11.1 (21.9)*	*8.4*	*0.12*	*5.20*	*0.29*
Permacol®	*65.2 (20.9)*	*67.2 (22.8)*	*2.7 (17.8)*	*(-2.4-19.3)*		*(-4.52-14.9)*	
EQ-5D index (-0.594 –1)							
SNM	*0.68 (0.20)*	*0.74 (0.20)*	*0.059 (0.20)*	*0.031*	*0.55*	*0.011*	*0.80*
Permacol®	*0.75 (0.18)*	*0.78 (0.14)*	*0.028 (0.19)*	*(-0.073-0.14)*		*(-0.074-0.095)*	
Urinary incontinence							
ICIQ-UI SF score (0-21)							
SNM	*11.3(6.45)*	*6.1 (6.12)*	*5.3 (5.8)*	*5.0x*	***0.002***	*3.04*	***0.037***
Permacol®	*6.9 (6.34)*	*6.4 (6.23)*	*0.27 (5.4)*	*(1.97-8.02)*		*(0.19-5.89)*	

*Values are mean (standard deviation). Difference in change (B) is reported as the mean (95% confidence interval) and was calculated with linear regression models, both unadjusted and *adjusted for baseline values. St Mark's incontinence score ranged from 0 (continent) to 24 (complete incontinence). FIQL= faecal incontinence quality of life. Its score ranged from 0 (worst) to 4 (best). Eq-5D= Euroqual 5-dimension. Eq-5D™ VAS ranged from 0 (worst) to 100 (best), and the index ranged from -0.594 (worst) to 1 (best). ICIQ-UI SF= International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form. It ranged from 0 (continent) to 21 (complete incontinence).*

Figure 1. Flow chart of enrolment into the study



SNM= sacral neuromodulation, PNE= Percutaneous nerve evaluation

Figure 2 The reduction of St Mark's score from baseline to six months in the SNM group compared to the Permacol® group