Gastrointestinal motility disorders in children: etiology and associated behaviors
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Sacral neuromodulation therapy: a promising treatment for adolescents with refractory functional constipation

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Abstract

Background: Sacral neuromodulation therapy has been successfully applied in adult patients with urinary and fecal incontinence and in adults with constipation not responding to intensive conservative treatment. No data, however, are available on sacral neuromodulation therapy as a treatment option in adolescents with refractory functional constipation.

Objectives: This study aimed to describe the short-term results of sacral neuromodulation in adolescents with chronic functional constipation refractory to intensive conservative treatment.

Design: This is a retrospective review.

Setting: This study took place at the Department of Surgery, Maastricht University Medical Centre, The Netherlands.

Patients: Thirteen patients (all girls, age 10 - 18 years) with functional constipation according to the ROME III criteria not responding to intensive oral and rectal laxative treatment were assigned for sacral neuromodulation.

Main outcome measures: When improvement of symptoms was observed during the testing phase, a permanent stimulator was implanted. Patients were prospectively followed up to at least six months after implantation of the permanent stimulator by interviews, bowel diaries, and Cleveland Clinic constipation score. Improvement was defined as spontaneous defecation ≥ 2 times a week.

Results: At presentation, none of the patients had spontaneous defecation or felt urge to defecate. All patients had severe abdominal pain. Regular school absenteeism was present in 10 patients. After the testing phase, all but 2 patients had spontaneous defecation ≥ 2 times a week with a reduction in abdominal pain. After implantation, 11 (of 12) had a normal spontaneous defecation pattern of ≥ 2 times a week without medication, felt urge to defecate, and perceived less abdominal pain without relapse of symptoms until 6 months after implantation. The average Cleveland Clinic constipation score decreased from 20.9 to 8.4. One lead revision and 2 pacemaker relocations were necessary.

Limitations: This study is limited by its small sample size, single-institution bias and retrospective nature.

Conclusion: Sacral neuromodulation appears to be a promising new treatment option in adolescents with refractory functional constipation not responding to intensive conservative therapy. Larger randomized studies with long-term follow-up are required.
Introduction

In children, the reported prevalence of constipation varies between 0.7% and 29.6%. Functional constipation occurs in all pediatric age groups, from newborns to young adults, and its severity may vary from mild and short-lived to severe and chronic with fecal impaction.

Children are considered to have functional constipation once organic causes such as anatomical or neurological abnormalities and endocrine or metabolic disorders are ruled out, and when they meet the ROME III criteria. These children are traditionally treated by a combination of laxative treatment and behavioral approaches, such as toilet training and education. Long-term follow-up studies have shown, however, that, despite intensive medical treatment, functional constipation persists into adulthood in 25 to 30% of children.

In those children with functional constipation not responding to maximal conservative treatment, more invasive surgical treatment options are often considered, such as colonic irrigation via a Malone antegrade continence enema or via a percutaneous endoscopic cecostomy. Unfortunately, these procedures are attended with substantial complication rates and, therefore, with relatively poor long-term success in children and adolescents. An alternative approach to bowel surgery in this group of young patients may be modulation of the extrinsic neural control of the large bowel or modulation of reflexes inhibiting large-bowel function. Electrical stimulation of sacral nerve roots has been shown to have a positive effect on peristalsis in the large bowel in patients with spinal cord injury. This stimulation can be achieved by the use of sacral neuromodulation (SNM) therapy. This minimally invasive surgical treatment has been successfully applied in adult patients with urinary and fecal incontinence and urinary retention. Recently, SNM therapy showed promising results in adults with functional constipation not responding to intensive conservative treatment. A large prospective multicentre study concluded that SNM therapy is an effective treatment of idiopathic slow- and normal-transit constipation in adults. No data, however, are available on SNM therapy in adolescents with refractory functional constipation.

Therefore, the aim of this manuscript is to describe results of SNM therapy in adolescents with chronic functional constipation refractory to intensive conservative treatment.

Methods

After Institutional Review Board approval, a retrospective study was performed investigating adolescents who underwent SNM therapy for constipation at the Maastricht University Medical Centre, The Netherlands. All patients were referred by the Emma...
Children’s Hospital/Academic Medical Centre in Amsterdam, The Netherlands, a tertiary referral center for children with severe organic and functional defecation disorders.

Constipation was defined according to the internationally accepted ROME III criteria for pediatric functional gastrointestinal disorders; the presence of at least 2 of the following criteria for at least 2 months prior to diagnosis; 1) 2 or fewer defecations per week, 2) at least 1 episode of fecal incontinence per week, 3) retentive posturing or stool retention, 4) painful or hard bowel movements, 5) presence of a large fecal mass in the rectum, 6) large diameter stools that may obstruct the toilet.²

To be eligible for percutaneous nerve evaluation (PNE) to assess feasibility of SNM therapy, patients had to fulfill Rome III criteria for functional constipation, not responding to intensive conservative treatment (oral laxatives, enemas or colonic lavage, and behavioral approaches). Patients were not eligible if they had organic pathology causing constipation, such as chronic IBD (Crohn’s disease or ulcerative colitis), or when they had a history of large-bowel surgery, congenital anorectal malformations, or neurological disease (complete spinal cord transection, multiple sclerosis, or spina bifida). Patients with significant psychological comorbidity (as judged by the investigator) or patients who were pregnant were also excluded.

In patients eligible for SNM therapy, history taking, physical examination, whole-gut transit time study, defecography, MRI of the lower pelvic area, anorectal manometry, and rectal sensitivity measurement were performed. Baseline evaluation included completion of a bowel habit diary during 21 consecutive days in which details on defecation frequency were recorded while the patient received optimal conservative therapy. The presence of abdominal pain, straining, and sensation of incomplete evacuation were rated by the patient as occurring “never”, “seldom”, “sometimes”, “often” or “always” in the preceding week.

Constipation severity was rated using the Cleveland Clinic constipation score. This score ranges from 0 - 30 with 0 indicating no symptoms and 30 indicating severe constipation as described by Agachan et al.¹¹ Absenteeism from school activities and total number of hospital admissions were also recorded.

Colonic transit time was assessed by the ingestion of radio-opaque markers and plain abdominal radiographs without the use of laxatives.¹² Defecography was performed by retrograde infusion of radio-opaque barium paste followed by the assessment of rectal configuration, perineal descent, and presence of structural or functional pathology before, during, and after evacuation.¹³

The lower pelvic area was imaged without sedation or anesthesia with either a Siemens Magnetom Avanto 1.5 T (Siemens AG, Erlangen, Germany) or a Philips Panorama 1.0 T (Philips Medical Systems, Best, The Netherlands) MRI system, depending on availability. Anorectal manometry (mean resting pressure and mean squeeze pressure) was performed by the use of a pull-through technique. Rectal sensitivity measurement included measurement of rectal volume and testing of the rectoanal inhibitory reflex.¹⁴
Consent was obtained by providing both patient and parents with all available information on therapy efficacy in adults, procedure and possible risks/benefits by different doctors on several occasions. Before resorting to an ileostomy or Malone stoma, risks (infection, scars) were acceptable to both patients and parents.

PNE and SNM procedure

The technique of the percutaneous nerve evaluation (PNE) procedure has been described in detail by Schmidt et al.15 SNM consists of 2 stages: a sub-chronic diagnostic stage (PNE) for which 2 options are available (temporary wire (Medtronic Interstim model 3057, Minneapolis, Minnesota, USA) or tined lead (Interstim model 3889)) and a subsequent definitive implant stage in which the implantable neurostimulator (INS; Interstim II model 3058) is implanted (without tined lead if previously in situ). The advantages of testing with a tined lead are less lead migration after placement and, therefore, a longer possible testing period. Another advantage is that the definitive implant stage only consists of connecting the INS with the tined lead and removing the extension cable. This procedure is performed under local anaesthesia.6 Local anesthesia is preferred because it allows for patient input during the procedure.16 Correct placement was confirmed by observing motor and/or sensory responses, i.e. pelvic floor contraction, great toe flexion, and/or paresthesia in the anal or vaginal region.15 A 3-week screening period then commenced with continuous stimulation during daytime at low-amplitude sensory threshold settings (pulse amplitude 0.4 - 2.7 V; pulse width, 210 μs; frequency, 16Hz). During this diagnostic stage, all patients completed a 3-week bowel habit diary to assess outcome. To be eligible for implantation of the INS, patients had to have experienced a subjective improvement of symptoms without the use of laxatives or enemas as recorded in their bowel habit diary. Next to this, an increase in bowel frequency as defined as spontaneous defecation ≥ 2 times a week and/or a decrease in the total number of episodes of straining, incomplete evacuation, and abdominal pain had to be present.10

The INS was subsequently implanted in a subcutaneous pocket in the buttock and attached to the quadripolar tined lead. Following this second stage, the therapeutic settings were programmed to sensory threshold, which is usually lower than the motor response threshold, and patients were taught to use their own handheld programmer.17 Patients were followed up at 1, 3, 6, and 12 months after permanent implantation. The efficacy was assessed by the Cleveland Clinic constipation score11 and a bowel habit diary. Use of additional laxatives or enemas and absenteeism from school were documented. Any undesirable symptom that occurred during the stimulation was documented as an adverse event, regardless of whether it was considered to be related to the treatment.
Statistics
Continuous variables are tested for normality of distribution by the Shapiro-Wilk test. Data are presented both as means, SD, median and score ranges if applicable. Categorical variables are given as frequencies and percentages.

In analyzing clinical measures in this cohort, each patient served as his or her own control, using baseline (optimal conservative treatment, care-as-usual) data compared with the outcome at each follow-up visit: at testing (screen), at 1 month after testing, at 3 months, at 6 months, and at 12 months after testing. At first, repeated measures ANOVA was performed up to 6 months of follow-up. Overall F-ratio tests are conservatively corrected for deviations from sphericity by Greenhouse-Geisser adaptations of the degrees-of-freedom. The weighted 6-month linear trend was calculated over all visits and tested for deviation from zero (no change). Next, a nonparametric analysis was performed using the Friedman test as an overall statistic and the Wilcoxon signed-rank test for testing differences between baseline and each follow-up visit. A $p$-value of less than 0.05 is considered to be statistically significant, but the low numbers of patients and the explorative nature of the cohort necessitate regarding the correlative results of this manuscript with both interest and care. All data analysis was done with SPSS for windows version 16.0 (SPSS Inc, Chicago, IL).

Results
A total of 13 girls with a median age of 15.2 years (range, 10-18) underwent PNE; 12 of these patients received a permanent implant between February 2009 and March 2010. One year follow-up was available in only five patients, and 6 months follow-up in all 12 patients. The median age at onset of symptoms was 5 years (range, 1 - 12 years). Median therapy duration at time of inclusion was 7 years (range, 1 - 17 years). At baseline in all patients, all possible laxatives and several combinations of conservative treatment had been administered. Ten patients used daily oral polyethylene glycol electrolyte bowel lavage (Klean-Prep, Norgine BV) up to 2 L (60 - 120 g of PEG 3350 per day), 2 patients frequently used enemas, and 1 patient used daily retrograde colonic irrigation. In 1 patient, laxatives were administered daily through a Malone appendicostomy.

Baseline Investigations
A colonic transit time study was performed in 9 patients (69%). Seven patients had slow transit constipation, and 2 had normal-transit constipation. Defecography was performed in 9 patients (69%). Five patients showed incomplete or no evacuation, and 3 patients had a radiological rectocele or outlet obstruction. Anorectal manometry was performed in 10 patients (77%) with normal anorectal parameters, including a normal rectoanal
inhibitory reflex, in all 10 patients. MRI was performed in 11 patients (85%). No anatomical abnormalities were found. At baseline, none of the patients had spontaneous defecation without medication. Defecation was only achieved by daily oral lavage or daily colonic irrigation.

**Outcome**

All patients but one treated in this cohort were evaluated with a tined lead during the testing stage. Twelve patients (92%) had a positive PNE test results and were consequently

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Descriptive statistics</th>
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<tbody>
<tr>
<td></td>
<td>Baseline(^a)</td>
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<tr>
<td><strong>Defecation frequency</strong></td>
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<td>Mean</td>
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<tr>
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<td><strong>Cleveland Clinic constipation</strong>(^c) (0-30)</td>
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<td>Mean</td>
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<td>SD</td>
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<tr>
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<tr>
<td>SD</td>
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<tr>
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<tr>
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<td>Maximum</td>
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<tr>
<td><strong>Incomplete evacuation</strong>(^d) (1-5)</td>
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All non-parametric tests between baseline and follow-up visits are statistically significant. \(^a\)Baseline data with optimal conservative treatment. \(^b\)Defecation frequency: episodes per week. \(^c\)Cleveland Clinic constipation: a score of 0 signifies no constipation and a score of 30 signifies severe constipation. \(^d\)Abdominal pain, straining, and incomplete evacuation: a score of 1 indicates ‘never’ and a score of 5 indicates ‘always’.
implanted with a pacemaker. PNE failed in 1 patient and the tined lead was explanted. Median follow-up was 7.3 months (range, 5.3 - 13.1). Descriptive statistics of all 12 patients undergoing implantation for defecation frequency, Cleveland Clinic constipation score, presence of abdominal pain, presence of straining, and sensation of incomplete evacuation measured at baseline and follow-up are presented in Table 1.
Repeated-measures ANOVA showed a statistically significant 6-months linear trend after implantation in the number of defecations (overall F-ratio = 5.33 by 2.4 and 26.5 \(df\), \(p = 0.008\) and linear trend effect F = 14.3 by 1 and 11 \(df\), \(p = 0.003\)), Cleveland Clinic constipation score (overall F-ratio = 49.3 by 1.4 and 15.3 \(df\), \(p<0.001\) and linear trend effect F = 155.0 by 1 and 11 \(df\), \(p<0.001\)), abdominal pain (overall F-ratio = 26.5 by 2.2 and 24.3 \(df\), \(p<0.001\) and linear trend effect F = 14.0 by 1 and 11 \(df\), \(p = 0.003\)), straining (overall F-ratio = 9.4 by 2.7 and 29.7 \(df\), \(p<0.001\) and linear trend effect F = 11.5 by 1 and 11 \(df\), \(p = 0.006\)) and sensation of incomplete evacuation (overall F-ratio = 6.1 by 2.3 and 25.6 \(df\), \(p = 0.005\) and linear trend effect F = 10.4 by 1 and 11 \(df\), \(p = 0.008\)) without any use of laxatives or colonic irrigation (Figs. 1 – 5).

**Figure 3** | Distribution of abdominal pain

**Figure 4** | Distribution of straining
The overall Friedman test p-value of weekly bowel movements over all visits was statistically significant (p<0.001). All Wilcoxon signed-rank tests between scores of baseline and follow-up were statistically significant (at screen p=0.003, at 1 month p=0.005, at 3 months p=0.002, and at 6 months p=0.004). The overall Friedman test p-values for the scores of the first half-year of the Cleveland Clinic constipation scale and the p-values for abdominal pain, straining and incomplete evacuation were all p<0.001 and p=0.001. Again, for each of these 4 outcome parameters, all Wilcoxon signed-rank tests between scores of baseline and follow-up measurements were statistically significant (all p-values <0.05, results not shown).

Use of additional laxatives or enemas was reported by 3 patients; 2 used laxatives or enemas only once, and 1 patient used enemas incidentally. Absenteeism from school was present in 10 patients (77%) at baseline and in none of the patients at 6-months follow-up. No admissions to the hospital were necessary during the first 6 months.

Three adverse events were documented in 3 patients (23%) who received a permanent implant. All adverse events were classified as minor events. Two patients experienced pain at the site of the pacemaker that was resolved by replacing the device in the buttock. One patient experienced an undesired change of sensation that could not be managed by reprogramming and subsequently required a lead revision. Lead revision was performed by implanting a new lead into the contralateral third sacral foramen with similar results on constipation.
Discussion

In our cohort, SNM appears to be a feasible option in treating constipation in adolescents not responding to optimal conservative treatment. Conservative therapy failed or was undesired in all patients. The creation of an ileostomy or a Malone stoma remained as the only alternative to SNM.

After implantation, a significant increase in defecation frequency and a significant decrease in abdominal pain frequency were observed in all patients. Results expressed by defecation frequency, Cleveland Clinic constipation score, abdominal pain, straining, and incomplete evacuation were maintained up to 6 months follow-up in all patients with a permanent implantation. In 5 patients, the 12-month follow-up was available and results persisted. These results were achieved without the daily use of laxatives or enemas, although a relapse of symptoms occurred in 3 patients, of which 2 needed laxatives only once. No hospital admissions were necessary after implantation.

Constipation in children and adolescents is usually treated by a combination of education, toilet training, and oral laxatives. Only in a minority of these patients, rectal clean outs or surgery are necessary. Long term results, however, of this approach are suboptimal. Staiano et al. have shown that chronic idiopathic constipation persists for more than 5 years in at least half of children treated conservatively. Moreover, others have shown that in at least 25% of children with functional constipation, symptoms persisted into adulthood. SNM therapy may therefore be a beneficial alternative treatment option. Kamm et al. showed a medium-term (1 – 55 months) success rate of 63% in adults with slow and normal constipation with a median age of 40 years. One patient in this study was 17 years-old. Viewed in this light, the high success rate of 92% in this cohort is remarkable. This may suggest that neuromodulation is more effective in younger patients.

This article reports data on the possibility of SNM therapy in a difficult patient group. Patients served as their own control. A randomized controlled trial is needed to provide clear insight in the efficacy of SNM now that these results indicate major benefit to the patient. Quality-of-life data should be assessed in future studies.

All PNE testing was performed under local anesthesia. In this age group, with the youngest patient being 10 years at the time of implant, general anesthesia may seem the obvious choice. However, we preferred local anesthesia to ensure perfect positioning of the lead based on sensory reaction to stimulation by the patient.

We used the tined lead in all but 1 patient. This provides the advantage of less lead migration after placement and, therefore, a longer possible testing period with better results than the temporary wire. Furthermore, permanent modulation is performed at the same lead position as during test stimulation. Another advantage is that the definitive implant stage only consists of connecting the INS and removing the extension cable. The downside of this approach is double the need for local anesthesia and increased risk of infection.
Because SNM therapy is a minimally invasive procedure and offers the possibility to test results before permanent implant, it seems a preferable approach to alternative surgical procedures for constipation. The reported pain in 2 patients was resolved by replacement of the pacemaker. Pain is a concern in SNM and has been described before.\textsuperscript{20, 21} Pain may be caused by mechanical pressure on the implanted device, or it may be due to the stimulation itself. In this cohort we have only used the smallest pacemaker available. In children and young adults, the thickness of the subcutaneous layer is usually less than in adults and positioning of the pacemaker during implantation should be done with extra attention to avoid possible future pain reports. Stimulation was predominantly felt in the leg by 1 patient. Although the results on constipation were good, we decided to replace the lead to another foramen because reprogramming could not relieve complaints. No infections were seen in these patients.

Providing insight in the success rate and occurrence of adverse events is difficult, because the exact working mechanism of SNM is still unknown. Rectal sensitivity has been described as unchanged, increased, or decreased.\textsuperscript{22-24} Changes in colonic transit time that have been described in both patients with fecal incontinence and constipation treated with SNM show seemingly contradicting results. SNM induces pancolonic propagating pressure waves and thus decreases colonic transit time in patients with constipation, whereas a reduced antegrade transport from the ascending colon and an increased retrograde transport from the descending colon at defecation have been described in fecal incontinence.\textsuperscript{25, 26} The effect of SNM on the colon may therefore be a result of neuromodulation at a more central level, and some studies have focused on corticoanal excitability in patients treated with SNM.\textsuperscript{27, 28, 29} Ismail et al have tried transcutaneous electrical stimulation in children with constipation, also achieving promising results.\textsuperscript{30} Nine of 11 (81%) showed improvement of symptoms. A preceding trial showed increased colonic transit and peristaltic activity, which suggests a possible parallel working mechanism with SNM.

**Conclusion**

SNM seems to be an effective short-term treatment in adolescents with chronic functional constipation refractory to intensive conservative treatment. These encouraging results with relatively minor adverse events stress the importance of further studies in larger patient groups with a longer follow up period. Furthermore, studies are necessary to unravel the underlying mechanisms of SNM.
References


