Neuromodulation: Technology at the Neural Interface

Received: May 25, 2022 Revised: July 24, 2022 Accepted: August 22, 2022

https://doi.org/10.1016/j.neurom.2022.08.451

Noninvasive Sacral Neuromodulation in Children and Adolescents: A Case-Control Study of Patients With Chronic Refractory Constipation

Sonja Diez, MD[1]; Annemarie Kirchgatter[1]; Dana Adam, MD[1]; Arne Füldner, MD[1]; Hanna Müller, MD[2]; Klaus E. Matzel, MD[3]; Manuel Besendörfer, MD[1]

ABSTRACT

Objectives: In adult patients with chronic refractory constipation, invasive sacral neuromodulation (SNM) has been applied successfully. There is a need for less invasive solutions while providing comparable therapeutic effects in children and adolescents. We present a prospective, interventional case-control study on the application of noninvasive SNM.

Materials and Methods: Patients with chronic constipation refractory to conservative treatment were prospectively included in the study from 2018 to 2021 and randomized to either SNM (SNM group: single current stimulation for 24 h/d, frequency 15 Hz, pulse width 210 μs, intensity 1–10 mA) or conventional treatment (controls: full range of pharmacologic and nonpharmacologic options). Treatment was conducted for 12 weeks. Treatment effects were collected with specialized questionnaires and quality-of-life analysis ($KINDL_R$). Outcome variables were defecation frequency, stool consistency, fecal incontinence (FI) episodes, and abdominal pain.

Results: Analysis was conducted in 28 patients with SNM and 31 controls (median age 7.0, range 3–16 years). Overall responsiveness to treatment was 86% of the SNM group and 39% of the control group ($p < 0.001$). All outcome variables were positively influenced by SNM treatment. Defecation frequency improved in 46% of patients with SNM and in 19% of controls ($p = 0.026$), as did stool consistency in 57% of patients with SNM and in 26% of controls ($p = 0.014$). Fecal incontinence was significantly reduced in 76% of patients with SNM ($n = 16/21$ vs 42% of controls [$n = 11/26$], $p = 0.042$). Quality of life improved significantly during SNM treatment (71.32 [baseline] vs 85.00 [after 12 weeks], $p < 0.001$) and confirmed a positive influence of SNM treatment compared with the control group (85.00 [SNM after 12 weeks] vs 79.29 [controls after 12 weeks], $p = 0.047$).

Conclusions: Outcome of noninvasive SNM treatment in patients with chronic refractory constipation is better than conventional treatment.

Keywords: Fecal incontinence, functional constipation, Hirschsprung disease, sacral nerve stimulation, sacral neuromodulation

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Neuromodulation has been in clinical use for more than 20 years, treating diverse pathologies within various clinical fields such as cardiology, urology, neurology, and gastroenterology. Neuromodulatory treatment of functional gastrointestinal disorders is especially expanding.[1] This might be due to the central role of sacral neuromodulation (SNM) in treatment of fecal incontinence (FI) and constipation.[2–4]

The implementation of neuromodulation therapy in pediatric patients remains challenging, though, on the basis of its invasive

Address correspondence to: Sonja Diez, MD, Department of Surgery, Section of Pediatric Surgery, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Loschgestrasse 15, 91054 Erlangen, Germany. Email: sonja.diez@uk-erlangen.de

[1] Department of Surgery, Section of Pediatric Surgery, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany;
[2] Department of Pediatrics, Neonatology and Pediatric Intensive Care, University of Marburg, Marburg, Germany; and
[3] Department of Surgery, Section of Coloproctology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please see the journal's Guide for Authors.

Source(s) of financial support: The authors reported no funding sources.

nature, considerable costs, and risk of complications. To balance these disadvantages, we are presenting a more flexible and secure approach to our pediatric patients: SNM is conducted through a transabdominal electrical field, which can be stopped and restarted at any time owing to adhesive electrodes and an external pacemaker.[1,5] We apply the parameters of the implantable SNM used in the treatment of constipation and FI in adults.[6] The goal is to achieve a physiological bowel movement by a continuous single current stimulation. The benefits of invasive SNM are therefore combined with the applicability at home, the individual therapeutic settings, and the low number of complications.

There are only a limited number of investigatory studies, focusing on lumbosacral, transcutaneous stimulation in the treatment of chronic constipation in children and adolescents.[6–10] All these published studies on noninvasive SNM are consistent in its success in approximately 75% of patients: improvement of defecation frequency and stool consistency, improved sensation of urge to defecate, reduction of episodes of FI and abdominal pain, and finally, improvement of quality of life.[1,11] To our knowledge, none of them elaborates the efficacy of noninvasive SNM compared with conventional options, which are, as an established part in the therapeutic algorithm of chronic constipation, comparable with noninvasive SNM regarding risks, flexibility, and application at home.

In this study, we thus present a case-control trial to compare the clinical efficacy of noninvasive SNM and conventional therapeutic options.

PATIENTS AND METHODS

Study Design

We prospectively recruited all participants of the study within the pediatric surgery department of our specialized center from 2018 to 2021. Patients are presented to our center in case of complex symptoms or failing standard therapy. The following criteria were applied for participation:

Inclusion criteria

- Age between two and 17 years
- Informed consent
- Chronic refractory constipation according to the Rome IV criteria for more than three months with or without encopresis/soiling[12]
- In cases of Hirschsprung disease: confirmation of diagnosis through rectal biopsies
- In cases of anorectal malformation or mechanical obstruction: postsurgical status

Exclusion criteria

- Patients with mechanical obstruction and the need for surgery in cases of underlying Hirschsprung disease or anorectal malformations
- Patients with constipation symptoms based on metabolic, inflammatory, and hormonal causes with further therapeutic options
- Neuronal malignancies under medical and radiation therapy
- Seizures

Patients were randomized in a permuted-block randomization—unblinded, 1:1 ratio—to receive transcutaneous SNM therapy (SNM group) or continuation of optimized conservative maintenance therapy (control group, below). The group assignment was determined by the study directors after eligibility check-up by the attending physicians and study directors. Assignment was not influenced by any clinical or diagnostic features. The study protocol was approved by the local ethics committee (Friedrich-Alexander-Universität Erlangen-Nürnberg, Number B19_20) and complied with the Declaration of Helsinki. Each patient and next of kin signed an informed consent for participation. The study was registered with clinicaltrials.gov (Identifier NCT04710433).

Treatment Options

All patients received nonpharmacologic management (education and conduction of toilet training for stool regulation, behavioral modification, and dietary interventions[13]). In addition, disimpaction with polyethylene glycol (PEG, 1.5–2 mg/kg/d for one–two weeks) and initiation of maintenance therapy (PEG, 0.2-0.4 mg/kg/d) were conducted before the study inclusion and continued throughout the study period in both groups. Supportive local applications such as saline enemas or stimulant laxatives (glycerin, bisacodyl) were possible and were applied according to the determination of the attending physicians.

Controls received the continuation of maintenance therapy, which was adapted and improved in regular check-ups. Patients with SNM received noninvasive SNM treatment with no change in maintenance therapy, described as follows.

Noninvasive SNM was applied as described previously.[6] Two adhesive electrodes are placed paravertebrally between level L1 and L4 and periumbilically. They are 50 × 50 mm in size, adhere to the skin by themselves, and do not require additional electrode gel because the adhesive surface is conductive. Adhesive components are polyacrylic acid, sodium hydroxide or caustic soda, pure water, glycerol, polyacrylamide, and accelerant. Replacement is needed every two to four days in children. The manufacturer allows multiple use.

An electrical field with a 15 Hz frequency, pulse width of 210 μs was applied with an external pulse generator. Noninvasive SNM was continuously applied for 12 weeks in each patient. The duration of stimulation was at least eight hours per day (recommendation for 24 h/d). Pauses for a few hours per day were possible, if needed. The stimulation intensity was determined individually at the start of the study by the attending physician: stimulation intensity was increased under direct response of the patient to a comfortable sensation (tingling paresthesia in the lower abdomen; in younger children, attending physicians looked for a "tickling" sensation) below pain threshold (adjustable amplitude 0–10 mA). Patients were advised to continue the SNM treatment with the set stimulation intensity. Adaption to therapy with a decrease in tingling paresthesia was possible during treatment. Change of pharmacologic treatment was not recommended during the study period.

According to the instructions of the manufacturer, allergic reactions to components of the adhesive are possible. In these cases, we switched to adhesive electrodes with other components or slightly changed the placement of the electrode.

Data Collection and Outcome Variables

We recorded demographic data and medical and surgical history of all patients with specialized questionnaires on chronic constipation disorders in children and adolescents. We developed these specialized questionnaires to collect data before the study. The two forms are 1) patients' history (defecation characteristics within the first year of life, development of defecation problems,

history of treatment and diagnostics, psychosocial stressors) and current symptoms and medication; and 2) patients' current symptoms and medication under treatment with noninvasive sacral neuromodulation, stimulation parameters, and evaluation of its subjective success. Selectivity and reliability of items are given because these questionnaires are applied and revised regularly. In addition, inconsistencies in collected data by attending physicians were revised and discussed directly with the patients. Results of diagnostic and therapeutic steps before the study were also identified. Clinical symptoms, medication, and stimulation parameters were collected in each patient before the start of the study, and after four, eight, and 12 weeks. The patients and their parents were also asked to complete bowel movement diaries during the study period. We always encouraged the patients to complete our specialized forms by themselves. Only in very young children were parents asked to represent patients.

Primary and secondary outcome variables were defined as presented in Table 1.

Treatment response of patients was assessed according to outcome variables. A clinically relevant improvement was defined in cases with at least two of four fulfilled criteria, achieving symptom control. Because results showed a great variety of defecation frequency in patients, not only normalization of frequency (1x/d) was estimated as clinically relevant response but also the duplication of episodes (eg, patient with a frequency of 1x/wk presented a clinically relevant response in case of improvement to defecation frequency of 3–4x/wk).

FI was diagnosed at the age of ≥ 4 years in cases of previous adequate toilet training and urinary incontinence at the age of ≥ 6 years with at least four episodes per week.

Quality of Life

Quality-of-life data were assessed before and after treatment using the "Revised Children's Quality of Life Questionnaire" ($KINDL_R$). This reliable and validated questionnaire is a self-report measurement for health-related quality of life in children and adolescents.[15,16] It consists of 24 five-point Likert-scale items, covering six quality-of-life dimensions: physical well-being, emotional well-being, self-esteem, family, friends, and daily functioning (school or nursery school/kindergarten). Items are partially reverse-scored and linearly transformed to a 0 to 100 scale according to the manual. The subscales of these six dimensions are combined to produce a total score. Higher scores indicate a better quality of life. The questionnaire is available in three age-specific versions (Kiddy-$KINDL_R$ for 4–7 years old, Kid-$KINDL_R$ for 8–12 years old, and Kiddo-$KINDL_R$ for 13–16 years old). We evaluated changes of patients with SNM during treatment (Table 2) and the comparison between patients with SNM and controls (Table 3).

Statistical Analysis

Statistical analyses were performed using SPSS (version 28; IBM, Armonk, NY). Categorical data are reported as frequencies and percentages in cases of demographic data and outcome variables. Outcome variables were presented as median and range in cases of ordinal scale values (defecation frequency, stool consistency, episodes of encopresis, and abdominal pain, Tables 4 and 5). Results of the quality-of-life analysis were presented as mean and standard deviation based on cardinal scale values. We compared clinical outcome data using chi-square and Fisher's exact tests at defined time points before and after treatment in both groups. Quality-of-life data were compared using the unpaired or paired, two-tailed sample *t*-tests, if applicable. Data are expressed as median and range or mean and SD. All p-values less than 0.05 were considered statistically significant.

RESULTS

Demographic Data of the Study Population

We identified 69 patients with chronic constipation in this prospective single-center study. All patients were treated from 2018 to 2021. The study design is depicted in Figure 1 and illustrates the primarily heterogeneous population of the study. Six patients withdrew from the study before the start of the therapeutic application (owing to the noncompliance of participants to therapy), and four more patients were lost to follow-up during treatment. According to the inclusion and exclusion criteria, 69 patients were identified for participation, of whom 59 were included in analyses: 28 were assigned to the SNM group and 31 to the control.

Children were aged from three to 16 years at time of therapy (median age 7.0 years). Owing to the study allocation process, sex distribution was equal in the whole study cohort but differed narrowly in comparison of the two groups. Patients' clinical characteristics are shown in Table 6. Although there are no significant differences between the study groups, we included a heterogeneous population to reflect the complex symptoms of the actual daily patient distribution.

Stimulation Parameters

The SNM stimulation parameters, set before the start of the treatment for every patient and not changed during treatment, were a frequency of 15 Hz and a pulse width of 210 μs. Patients

Table 1. Primary and Secondary Outcome Variables and Measurements.

Variable	Measurement	Definition of response
Primary outcome		
Defecation frequency	Number of bowel movements/wk	Duplication of episodes/wk
Stool consistency	Daily assessment of Bristol Stool Scale[14]	Change of at least 2 points within the scale of 1–7
Episodes of fecal incontinence	Number of episodes of fecal incontinence/wk	Reduction by at least 50% of episodes/wk
Episodes of abdominal pain	Number of episodes of abdominal pain/wk	Reduction by at least 50% of episodes/wk
Secondary outcome		
Improvement of sensation of urge to defecate	As mentioned in the specialized questionnaires	
Episodes of urinary incontinence	Number of episodes of urinary incontinence/wk	Reduction by at least 50% of episodes/wk

The table presents the outcome variables of the study with the according measurements and definition of response.

Table 2. Quality-of-Life Analysis of Patients With SNM.

$KINDL_R$ dimensions	Baseline SNM cases (n = 28)		12 wk SNM cases (n = 28)		p Value
	Mean	± SD	Mean	± SD	
Physical well-being	67.41	± 15.44	85.00	± 17.59	< 0.001
Emotional well-being	74.78	± 17.55	88.62	± 10.63	< 0.001
Self-esteem	67.19	± 16.46	83.93	± 16.35	< 0.001
Family	79.69	± 15.83	87.95	± 12.95	0.022
Friends	66.07	± 16.53	83.26	± 13.72	< 0.001
Daily school functioning	73.84	± 18.18	85.88	± 14.25	0.009
Total score on quality of life	71.32	± 10.73	85.00	± 10.75	< 0.001

The table presents the data on quality of life in patients under SNM treatment according to the $KINDL_R$ questionnaire, compared between baseline and end point of the study (12 weeks of treatment). Significance: $p < 0.05$.

were able to adjust treatment stimulation intensity and duration of application. We observed a median stimulation intensity of 6.0 mA (range 2–8 mA), which was determined by the attending physician at the start of SNM treatment and was not changed during treatment of every patient. Twenty-three of 28 patients (82%) applied SNM treatment for >12 hours per day (range 8–24 h); only five patients (18%) used it for fewer than 12 hours per day. The duration of treatment was changed individually based on daily life activities.

Clinical Symptoms in Course of Treatment: Outcome Variables

All patients enrolled in the study fulfilled the Rome IV criteria for chronic functional constipation and showed classical symptoms refractory to nonpharmacologic treatment and medication with oral or rectal laxatives. Baseline symptoms and results of primary and secondary outcome variables are shown in Tables 4, 5, and 7. Overall responsiveness as defined above—at least two criteria of primary outcome variables reached—was achieved in 86% of patients with SNM (n = 24) and 39% of the control group (n = 12).

SNM influenced at least one primary outcome variable in every patient. All responders of the SNM group recommended this therapeutic option to other affected children.

Negative impact or adverse events on constipation symptoms were not observed. Adverse effects occurred rarely: micturition abnormalities in two patients (7%), with urinary dysfunction before treatment and cutaneous allergic reactions in four patients (14%). These allergic reactions were limited to skin exanthema with itching and occurred on both the ventrally and dorsally attached electrode. We evaluated this as a local reaction to adhesive components and for example, sweat. This could easily be treated by changing the electrodes to ones with other adhesive components and the slight alteration of location.

Twenty-one of 28 patients with SNM (75%) and 26 of 31 controls (84%) also suffered from FI. A clinically relevant improvement as defined above was seen in 16 patients with SNM (57%) and 11 controls (35%) compared with baseline. In two patients of the SNM group and one control, FI occurred at the age of three years. These patients were not included in the FI group but were counted as clinically relevant–improved in case of positive influence on incontinence episodes and support in toilet training under therapy. Secondary diagnoses included urinary incontinence in 43% of the patients in the SNM group (n = 12) and 16% of the controls (n = 5). Only SNM treatment was reported to influence urinary incontinence in three cases (25%) positively.

Dosage of oral medication did not differ in a comparison of the two study groups. Patients were advised not to change medication during treatment. However, in 13 patients of the SNM group (46%), reduction of medication was advised under SNM treatment because defecation frequency and consistency were exaggerated to high frequencies (> 3 times/d) and changed to fluid consistency (Bristol Stool Scale 7). In these patients, laxatives were reduced or even terminated during treatment, resulting in symptom-free patients. Medication was not changed in any patient before the eighth week of therapy.

Primary and secondary outcome variables were also separately analyzed in patients with Hirschsprung disease: 11 of 13 patients with SNM (85%) responded positively to treatment, whereas

Table 3. Quality-of-Life Analysis of Study Population.

$KINDL_R$ dimensions	SNM cases (n = 28)		Controls (n = 31)		p Value
	Mean	± SD	Mean	+/- SD	
Physical well-being	85.00	± 10.75	79.29	± 10.26	0.047
Emotional well-being	88.62	± 10.63	82.81	± 14.40	0.092
Self-esteem	83.93	± 16.35	75.37	± 18.51	0.074
Family	87.95	± 12.95	84.38	± 14.08	0.328
Friends	83.26	± 13.72	77.23	± 12.41	0.090
Daily school functioning	85.88	± 14.25	79.81	± 13.61	0.119
Total score on quality of life	85.00	± 10.75	79.29	± 10.26	0.047

The table presents the data on quality of life in patients according to the $KINDL_R$ questionnaire, compared between SNM cases and controls at end point of the study (12 weeks of treatment). Significance: $p < 0.05$.

Table 4. Primary Outcome Variables: Responsiveness to Treatment.

Clinically significant improvement compared with baseline in	SNM cases (n = 28)	Controls (n = 31)	p Value
Overall responsiveness, ≥ 2 fulfilled primary outcome variables, n (%)	24 (86%)	12 (39%)	< 0.001
Defecation frequency, n (%)	13 (46%)	6 (19%)	0.026
Defecation consistency, n (%)	16 (57%)	8 (26%)	0.014
Fecal incontinence, n (%)	n = 21 16 (76%)	n = 26 11 (42%)	0.042
Abdominal pain, n (%)	20 (71%)	9 (29%)	0.001

clinically significant improvement was only seen in one of six controls (17%, $p = 0.010$). Analysis regarding age groups also revealed no significant differences in SNM effects.

In addition, a model of an intention-to-treat analysis was conducted within the analysis, which could confirm the presented results above. Twenty-four of 32 patients with SNM (75%) and 12 of 37 controls (32%) responded to therapy based on the determined criteria ($p < 0.001$).

Quality of Life

We assessed the quality of life according to the $KINDL_R$ measurement by evaluating the treatment effect of SNM and comparing the two study groups. Evaluation of quality of life during SNM showed significant improvement of physical well-being ($p < 0.001$) and emotional well-being ($p < 0.001$), self-esteem ($p < 0.001$), satisfaction in relationships with family ($p = 0.022$) and friends ($p < 0.001$), and daily life functioning ($p = 0.009$). This resulted in a significant overall improvement of the total quality of life score (71.32 [baseline] vs 85.00 [after 12 weeks], $p < 0.001$). Results are summarized in Table 2.

Baseline analysis of quality of life did not differ between the two study groups before the study (total quality of life score of SNM cases 71.56 vs controls 74.72, $p = 0.419$). We evaluated quality of life after 12 weeks: patients in the SNM group showed an outcome in total quality-of-life score ($p = 0.047$, Table 3) significantly better than that in the control group. Further evaluation of quality-of-life scores in correlation with different demographic and clinical factors (such as age, diagnosis, previous surgeries) was conducted but failed to achieve statistical significance in most aspects (Table 8). A significance of improved total quality of life in cases of Hirschsprung disease was seen under SNM treatment ($p = 0.047$).

DISCUSSION

After promising results of a pilot study,[6] we present a prospective interventional case-control study applying noninvasive SNM in children and adolescents. We can confirm an overall efficacy of noninvasive SNM in combination with pharmacologic and nonpharmacologic options in 86% of patients. To our knowledge, this is the first study comparing SNM treatment with standard conventional options in childhood constipation.

For therapy of chronic childhood constipation, there is a desperate need for more efficient options of maintenance therapy. Although most patients reach symptom control with conventional treatment options, up to 20% to 30% of patients with a variety of different underlying diagnoses are refractory to those treatment options.[17,18] This is especially important because further surgical therapeutic options, such as Malone ostomy or other ostomies, often lead to irreversible states and high risks due to surgical complications.[19,20] They should thus be considered as a last resort.[21] Almost 10% of patients with intractable constipation, though, are estimated to need surgical intervention in the course of treatment.[22]

We see the great value of childhood sacral neuromodulation in bridging this gap between conventional and surgical options for patients with constipation refractory to conservative treatment.

Influence of SNM on Clinical Symptoms

We were able to show a therapeutic option to improve defecation frequency and stool consistency while reducing abdominal pain episodes. In addition, an improved sensation of urge to defecate can be observed in our patients. Transcutaneous electric stimulation of the second and third sacral nerve roots, innervating the bladder, rectum, and pelvic floor, activates potential targets such as sacral sensory and motor nerves, enteric nerves, and sympathetic and parasympathetic nerves, in addition to intestinal muscle cells and vessels to improve mobility and perfusion.[1,9] An effect on the neuroplasticity of the enteric nerves has also been suggested.[11]

On the basis of the case-control design of our study, we were able to show an added therapeutic benefit of SNM in combination with conventional therapy vs conventional therapy alone. However, it is noteworthy that there is a selection bias within our study population based on patients with chronic refractory symptoms. Given both groups consist of patients refractory to treatment, we

Table 5. Secondary Outcome Variables.

Variable	SNM cases (n = 28) with improvement since baseline	Controls (n = 31) with improvement since baseline	p Value
Urinary incontinence/wk, n (%)	n = 12 3 (25%)	n = 5 0	0.521
Perception of urge, n (%)	23 (82%)	10 (32%)	< 0.001

The tables show a comparison of baseline and end-of-therapy variables in comparison with cases with SNM and controls. p Values are calculated with the chi^2-test or Fisher's test, if applicable, and measure the comparison between SNM and controls at the end of the 12-week treatment period. Significance: $p < 0.05$.

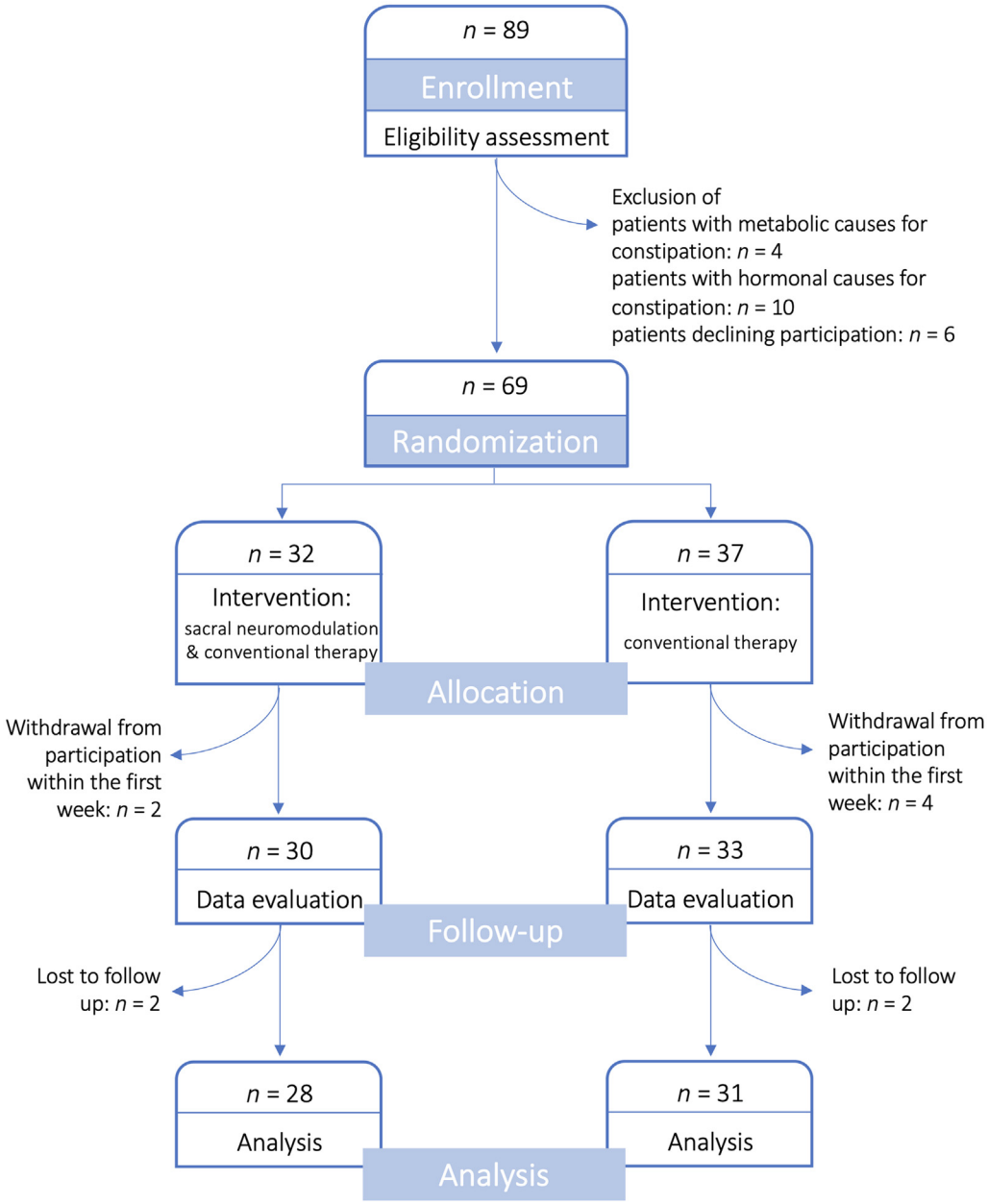

Figure 1. Study design and participation of 69 patients. [Color figure can be viewed at www.neuromodulationjournal.org]

obtain a comparable baseline while offering specific treatment to only one group. This should be considered in the interpretation of the presented data.

Conventional therapy with optimal pharmacologic, behavioral, and psychologic options has been established over many years and shows therapeutic sufficiency within our study population, but still leaves a certain percentage with refractory symptoms. In these cases, the additional approach with SNM might control remaining symptoms and improve the quality of life significantly.

Influence of SNM on Quality of Life

Furthermore, our results reveal a significant benefit of SNM therapy in physical well-being and total quality of life scores. Patients suffering from chronic constipation are presenting comparably low quality-of-life scores as patients with oncologic diagnoses,[23] which can be confirmed by low quality-of-life levels at baseline in our study. We failed to reach statistical significance in every category of quality-of-life analysis, which might be due to the small population. However, causes of the quality-of-life improvement during therapy cannot be fully elucidated with this study design.

The Study's Limitations

We performed a randomized interventional case-control study on SNM in children and adolescents with refractory chronic constipation. However, there are certain limitations.

Firstly, we decided to include a heterogeneous population regarding age and diagnoses because we aimed at reflecting the actual daily patient distribution of our center. However,

Table 6. Baseline Demographic Data of Study Population.

Demographic variable	SNM cases (n = 28)		controls (n = 31)		p Value
Age, median in y (range)	7.0 (3–16)		7.0 (3–14)		1.000
Sex, n (%)					0.787
Female	9	(32%)	11	(35%)	
Male	19	(68%)	20	(65%)	
Diagnosis, n (%)					0.083
Chronic Functional constipation	13	(46.5%)	21	(68%)	
Hirschsprung disease	13	(46.5%)	6	(19%)	
Congenital malformations	2	(7%)	4	(13%)	
Perianal/rectal surgical interventions before study, n (%)					0.266
Yes	10	(36%)	7	(23%)	
No	18	(64%)	24	(77%)	
Perianal Botox injections, M. sphincter ani externus et internus, n (%)					0.409
Yes	4	(14%)	2	(6%)	
No	24	(86%)	29	(94%)	
Medication, n (%)					0.496
Oral (PEG, Prucaloprid, Lactulose)	22	(79%)	26	(84%)	
Rectal (saline/nonsaline enema, Lecicarbon, anal irrigation therapy)	2	(7%)	0		
Both	2	(7%)	3	(10%)	
None	2	(7%)	2	(6%)	
Fecal incontinence, n (%)					0.521
Yes	21	(75%)	26	(84%)	
No	7	(25%)	5	(16%)	
Urinary incontinence, n (%)					0.042
Yes	12	(43%)	5	(16%)	
No	16	(57%)	26	(84%)	

The table shows a comparison of cases with SNM and controls. p Values are calculated with the chi^2-test or Fisher's test, if applicable. Significance: $p < 0.05$.

differentiation of functional constipation according to its pathogenesis such as to metabolic disorders, congenital colorectal malformations (Hirschsprung disease, anorectal malformations), and sacral nerval dysfunctions (meningomyelocele, sacrococcygeal teratoma, defecation dyssynergies) might be essential. Of these, postsurgical patients with Hirschsprung disease present in up to 45% of instances with long-term dysfunctional bowel pattern (obstruction, functional FI).[24,25] However, an underlying neuronal dysfunction is postulated to unite defecation disorders.[24] Furthermore, patients were randomly assigned to the SNM and the control group in a 1:1 allocation (permuted-block randomization) to balance the group sizes and possible influencing factors. Moreover, it seems that the SNM group starts out worse than the compared controls regarding FI and abdominal pain, although there were no significant differences between the study groups. This restricts strong conclusions, and enlarged population-based studies must validate our results.

Table 7. Study Outcomes: Primary Outcome Variables (Clinical Parameters).

Primary outcome variable	SNM cases	Controls
Defecation frequency, median episodes/wk		
Baseline	3	3
After 12 wk	7	5
Defecation consistency, median Bristol Stool Scale		
Baseline	5	4
After 12 wk	5	5
Fecal incontinence, median episodes/week		
Baseline	7	3
After 12 wk	3	3
Abdominal pain, median episodes/wk		
Baseline	7	3
After 12 wk	3	3

Objectivation of data in childhood constipation and FI remains challenging. It is noteworthy that despite its different pathogenesis, childhood constipation is always triggered by an interaction of behavioral and physiologic factors and is often accompanied by pseudo-incontinence due to overflow.[26] In addition, it is mainly influenced by therapy with high amounts of PEG, which is applied as standard fecal disimpaction and maintenance therapy without a standardized assessment of causes in pediatric patients by treating pediatricians.[21] We decided to positively value an influence on stool frequency and especially consistency in either direction.

The presence of multiple symptoms and the application of several therapeutic options challenge the interpretation of our data. The present study does not allow the drawing of conclusions on the reasons for symptom control. The impact of SNM on intestinal peristalsis may be the trigger for conventional options to improve their efficacy. However, abandoning standard conventional therapy options before SNM treatment was not an option for us in this population with refractory and high-burden conditions.

Follow-up of the study is limited owing to its short-term nature. An extrapolation to longer-term results may be difficult and must be elaborated in further studies. However, we saw an improvement of symptoms in every patient within three months of treatment, even if symptoms were not completely resolved. Further studies are planned to additionally evaluate the sustaining effects after discontinuation of SNM, as seen in previously published trials,[8] and

Table 8. Qualitys-of-Life Analysis of the Study Subgroups.

Quality of life in cases of	Total score of SNM cases (n = 28)	Total score of controls (n = 31)	p Value
	Mean ± SD	Mean ± SD	
Sex			
Female	(n = 9)	(n = 11)	0.041
	90.93 ± 8.44	78.75 ± 12.95	
Male	(n = 19)	(n = 20)	0.382
	82.45 ± 11.00	79.55 ± 9.11	
Diagnosis			
Functional constipation	(n = 13)	(n = 21)	0.693
	78.53 ± 9.25	79.99 ± 11.02	
Hirschsprung disease	(n = 13)	(n = 6)	0.047
	89.89 ± 9.05	77.43 ± 6.36	
Congenital malformations	(n = 2)	(n = 4)	0.082
	95.31 ± 6.63	77.03 ± 9.83	
Perianal/rectal surgical interventions before study	(n = 10)	(n = 7)	0.064
	89.35 ± 9.43	74.90 ± 1.62	
Fecal incontinence	(n = 21)	(n = 26)	0.142
	85.11 ± 11.10	80.59 ± 8.60	
Urinary incontinence	(n = 12)	(n = 5)	0.436
	80.56 ± 10.68	81.25 ± 6.32	

The table presents the data on quality of life in patient subgroups according to the $KINDL_R$ questionnaire. Significance: $p < 0.05$.

the effects of reapplication after relapse of symptoms. More data on cross-over patients (eg, patients receiving SNM treatment after conventional options failed) are being collected.

Finally, the easily perceptible treatment might be better comprehensible, especially for children, than conventional therapeutic options. This might trigger a certain positive psychologic effect, which influences the therapeutic success and might lead to a bias in the assessment of results. The influence of a potential placebo effect can thus not be excluded owing to the study design.

CONCLUSIONS

In conclusion, this prospective comparison confirms that SNM in its noninvasive approach can add a valuable option to the treatment of chronic refractory constipation in children. Treatment of constipation symptoms in childhood and adolescence is challenging. Conventional options are of high value and adequately treat most patients. However, patients with refractory symptoms suffer high levels of distress, and more options are needed. In combination with pharmacologic and nonpharmacologic treatment options, SNM appears to be superior to conventional options alone. We hypothesize that the effects are independent of the underlying etiologies. Prospective, randomized trials within larger, more homogeneous cohorts are needed to assess evidence-based treatment options for children with intractable constipation and functional FI. Given the potential influence on neuroplasticity, patients with Hirschsprung disease may especially benefit from early SNM, which also prompts further investigation.

Authorship Statements

Sonja Diez, Klaus E. Matzel, and Manuel Besendörfer designed and conducted the study, including patient recruitment, data collection, and data analysis. Annemarie Kirchgatter, Arne Füldner, and Dana Adam conducted data collection and data analysis. Sonja Diez prepared the manuscript draft, with important intellectual input from Arne Füldner, Hanna Müller, and Manuel Besendörfer. The revision process was mainly designed by Hanna Müller and Klaus E. Matzel. Sonja Diez, Arne Füldner, and Manuel Besendörfer had complete access to the study data. All authors approved the final manuscript.

How to Cite This Article

Diez S., Kirchgatter A., Adam D., Füldner A., Müller H., Matzel K.E., Besendörfer M. 2022. Noninvasive Sacral Neuromodulation in Children and Adolescents: A Case-Control Study of Patients With Chronic Refractory Constipation.
Neuromodulation 2022; ■: 1–9.

REFERENCES

1. Moore JS, Gibson PR, Burgell RE. Neuromodulation via interferential electrical stimulation as a novel therapy in gastrointestinal motility disorders. *J Neurogastroenterol Motil*. 2018;24:19–29.
2. Matzel KE, Stadelmaier U, Besendörfer M. Sacral nerve stimulation. *Acta Chir Iugosl*. 2004;51:49–51.
3. Maeda Y, O'Connell PR, Lehur PA, Matzel KE, Laurberg S, European SNS Bowel Study Group. Sacral nerve stimulation for faecal incontinence and constipation: a European consensus statement. *Colorectal Dis*. 2015;17:O74–O87.
4. Martellucci J. Sacral nerve stimulation for constipation: history of an unconsummated marriage. *Tech Coloproctol*. 2017;21:257–258.
5. Lu ML, He J, Lu S. Electrical stimulation therapy for slow transit constipation in children: a systematic review. *Int J Colorectal Dis*. 2015;30:697–702.
6. Besendörfer M, Kohl M, Schellerer V, Carbon R, Diez S. A pilot study of non-invasive sacral nerve stimulation in treatment of constipation in childhood and adolescence. *Front Pediatr*. 2020;8:169.
7. Chase J, Robertson VJ, Southwell B, Hutson J, Gibb S. Pilot study using transcutaneous electrical stimulation (interferential current) to treat chronic treatment-resistant constipation and soiling in children. *J Gastroenterol Hepatol*. 2005;20:1054–1061.

8. Leong LC, Yik YI, Catto-Smith AG, Robertson VJ, Hutson JM, Southwell BR. Long-term effects of transabdominal electrical stimulation in treating children with slow-transit constipation. *J Pediatr Surg*. 2011;46:2309–2312.
9. Yik YI, Hutson J, Southwell B. Home-based transabdominal interferential electrical stimulation for six months improves paediatric slow transit constipation (STC). *Neuromodulation*. 2018;21:676–681.
10. Coelho GM, Machado NC, Carvalho MA, et al. A protocol for an interventional study on the impact of transcutaneous parasacral nerve stimulation in children with functional constipation. *Med (Baltim)*. 2020;99:e23745.
11. Iacona R, Ramage L, Malakounides G. Current state of neuromodulation for constipation and fecal incontinence in children: a systematic review. *Eur J Pediatr Surg*. 2019;29:495–503.
12. Schmulson MJ, Drossman DA. What is new in Rome IV. *J Neurogastroenterol Motil*. 2017;23:151–163.
13. Levy EI, Lemmens R, Vandenplas Y, Devreker T. Functional constipation in children: challenges and solutions. *Pediatr Health Med Ther*. 2017;8:19–27.
14. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32:920–924.
15. Ravens-Sieberer U, Bullinger M. Assessing health-related quality of life in chronically ill children with the German KINDL: first psychometric and content analytical results. *Qual Life Res*. 1998;7:399–407.
16. Ravens-Sieberer U, Erhart M, Wille N, Bullinger M, BELLA study group. Health-related quality of life in children and adolescents in Germany: results of the BELLA study. *Eur Child Adolesc Psychiatry*. 2008;17(suppl 1):148–156.
17. Hasosah M. Chronic refractory constipation in children: think beyond stools. *Glob Pediatr Health*. 2021;82333794X211048739.
18. Sood M, Lichtlen P, Perez MC. Unmet needs in pediatric functional constipation. *Clin Pediatr (Phila)*. 2018;57:1489–1495.
19. Bharucha AE, Wald A. Chronic constipation. *Mayo Clin Proc*. 2019;94:2340–2357.
20. Siminas S, Losty PD. Current surgical management of pediatric idiopathic constipation: a systematic review of published studies. *Ann Surg*. 2015;262:925–933.
21. Leung AK, Hon KL. Paediatrics: how to manage functional constipation. *Drugs Context*. 2021;102020-11-2.
22. Sugarman I. Treatment of severe childhood constipation with restorative proctocolectomy: the surgeon's view. *Arch Dis Child*. 2010;95:861–862.
23. Clarke MC, Chase JW, Gibb S, Hutson JM, Southwell BR. Improvement of quality of life in children with slow transit constipation after treatment with transcutaneous electrical stimulation. *J Pediatr Surg*. 2009;44:1268–1272 [discussion: 1272].
24. Ladi-Seyedian SS, Sharifi-Rad L, Manouchehri N, Ashjaei B. A comparative study of transcutaneous interferential electrical stimulation plus behavioral therapy and behavioral therapy alone on constipation in postoperative Hirschsprung disease children. *J Pediatr Surg*. 2017;52:177–183.
25. Dariel A, Grynberg L, Auger M, et al. Analysis of enteric nervous system and intestinal epithelial barrier to predict complications in Hirschsprung's disease. *Sci Rep*. 2020;10:21725.
26. Nurko S, Scott SM. Coexistence of constipation and incontinence in children and adults. *Best Pract Res Clin Gastroenterol*. 2011;25:29–41.