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Long-term outcome of intractable constipation treated by sacral neuromodulation: a comparison between children and adults

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Abstract

Aim Sacral neuromodulation (SNM) is a minimally invasive therapy for functional constipation (FC) and is most often used to treat adults. Recent studies suggest that SNM may also be beneficial in children. However, comparative data regarding preferred age of SNM for FC are lacking. Therefore, long-term results of SNM for FC were compared between children and adults.

Method All patients treated with SNM for FC between 2004 and 2015 were evaluated. Outcomes of children (age 10–18 years) were compared with those for adults (≥ 18 years). The primary end-point was a defaecation frequency of three or more times per week, which is consistent with the ROME-III criteria. Secondary outcomes were quality of life (QoL; SF-36) and the Cleveland Clinic Constipation Score.

Results One hundred and eighty patients (45 children, 135 adults) were eligible for SNM. The mean age was 15.8 (children) and 41.4 years (adults). One hundred and twenty-six patients received permanent SNM (38 children, 88 adults). Mean follow-up was 47 months in both groups. Defaecation frequency increased in both groups after SNM compared with baseline. Defaecation

frequency in adults was higher than in children. The increased defaecation frequency was maintained during the entire follow-up period in both groups. QoL of children was impaired compared with the Dutch population with regard to bodily pain, general health and vitality. Adults had worse QoL with regard to physical functioning, bodily pain, general health, vitality and social functioning compared with the Dutch population. QoL of children did not differ from adults.

Conclusion Sacral neuromodulation (SNM) should be considered in children (< 18 years) with FC. However, the indication of SNM for FC remains debatable considering the limited improvements and high costs.

Keywords Sacral neuromodulation, constipation, children, adults, quality of life

What does this paper add to the literature?

It is unknown whether sacral neuromodulation (SNM) is as effective in the treatment of functional constipation (FC) for children as for adults. This study demonstrates that SNM should be considered for children with FC as the procedure is safe and feasible with comparable long-term outcomes to those in adults.

Introduction

Constipation is a common functional gastrointestinal disorder with a prevalence varying from 19% to 30% in

the general population [1] and from 0.7% to 29.6% in children [2]. Constipation has a significant impact on the quality of life (QoL) of both patients and their families [3]. Treatment of functional constipation (FC) still poses a great challenge as one-third of patients do not respond to current conservative therapies [4,5]. A minority of these patients undergo major surgery such as a colostomy or colectomy. However, these procedures are invasive, irreversible and associated with high morbidity (20%) and mortality (2.6%) [6–8].

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Sacral neuromodulation (SNM) is a relatively novel, minimally invasive surgical therapy for FC and works through electrical stimulation of the third sacral nerve. Success rates of SNM for FC in both children and adults are controversial. Some studies have reported success rates of 52%–87% and 84.6%–90% in children and adults, respectively [9–14]. However, these positive results are at variance with other studies which report success-rates of 27.3%–29.0%, which according to the authors are associated with a placebo effect [15–17]. The large variation in outcomes between children and adults might be related to different aetiologies of FC in each age group and the use of different primary outcome parameters [2].

Despite the increasing use of SNM for FC, knowledge regarding the effect of age on the efficacy of SNM for FC remains unclear. Moreover, comparative data regarding long-term outcomes between children and adults are essential to optimize the timing of SNM. Therefore the aim of this study is to compare long-term results of SNM for FC between children and adults.

Method

All patients who underwent SNM for FC between 2004 and 2015 were retrospectively reviewed. All patients had failed conservative treatment prior to evaluation.

Inclusion criteria

Children between 10 and 18 years and adults ≥ 18 years of age were included if symptoms of FC existed for at least 3 months prior to visiting our outpatient clinic and if all conservative treatments such as laxatives, suppositories, enemas, retrograde irrigation and biofeedback therapy failed. Constipation was defined according to the ROME III criteria for children [18] and adults [19].

Exclusion criteria

Patients were excluded if they suffered from irritable bowel syndrome with constipation (IBS-C) or IBS with alternating type (IBS-A) [19], neurological pathology (e.g. spinal cord transection, multiple sclerosis or Parkinson's disease), a psychiatric or psychological comorbidity or if they had a stoma *in situ*. Patients who were pregnant or those attempting to become pregnant were also excluded. Patients born with a spina bifida who were able to walk were not excluded.

Assessment

Baseline evaluation consisted of a standardized 3-week bowel habit diary, Cleveland Clinic Constipation Score

(CCCS) [20], anorectal manometry and defaecography. All children and adults completed this baseline evaluation. The bowel habit diary was used to assess the defaecation frequency, presence of straining and use of laxatives or enemas to stimulate defaecation. Adults were also asked for sensation of incomplete evacuation and abdominal pain and bloating. Children were asked regarding faecal incontinence and withholding behaviour. For preference patients filled in the bowel habit diaries without the use of laxatives. Patients were allowed to take laxatives if they had no defaecation for more than 2 days.

The CCCS was used to assess the severity of FC in both children and adults and consists of a score from 0 (no symptoms) to 30 (severe symptoms). A lower score indicates lower severity of FC.

Anorectal manometry was performed to evaluate the rectal sensation threshold and to elicit the rectoanal inhibitory reflex to rule out Hirschsprung's disease. Defaecography was used to assess anorectal configuration, pelvic floor position and the presence of structural or functional abnormalities. Colon transit time studies were not performed for every patient and were therefore not included in this study.

Surgical procedure

The surgical technique for SNM was previously described and consists of a two-stage procedure [21]. The surgical procedures were conducted under local or general anaesthesia by an experienced surgeon. Children and adults were operated on by the same surgeons. In short, anatomical landmarks, fluoroscopy and a testing needle were used to identify the correct sacral foramen. Correct placement of the needle was confirmed by contraction of the pelvic floor. Afterwards a temporary unipolar percutaneous nerve evaluation (PNE)-lead (Medtronic Interstim model 3057, Minneapolis, Minnesota, USA) or a tunnelled, quadripolar tined lead (Medtronic Interstim model 3093/3889) was inserted which was connected to an external stimulator (Medtronic model 3625 or 3531). A PNE-lead was used up to 2007, and only in adults. From 2008 onwards, all patients received a tined lead. Both PNE and TLP were followed by a 4-week test-period during which continuous stimulation was applied using standard settings (amplitude 0.1–10 V, pulse width 210 μ s, frequency 16 Hz). The stimulation settings were optimized during the first week of the 4-week test-period. During the following 3 weeks patients completed the 3-week bowel habit diary.

After the test-period, the PNE-leads were removed. A tined lead was left *in situ* in case of a positive result. Patients were eligible for permanent implantation in

case of a defaecation frequency of three or more times per week after the SNM-screening period based on the 3-week bowel habit diary.

For a PNE lead, an electrode fixed to the sacrum was inserted in the same foramen as the PNE lead and connected to a permanent implantable pulse generator (IPG) which was implanted under general anaesthesia. For a tined-lead, the IPG was mostly implanted under local anaesthesia. Based on the patient's age, amount of subcutaneous tissue and applied current, one of two types of IPGs was implanted in a subcutaneous gluteal pocket under antibiotic cover. The larger neurostimulator (Medtronic Interstim model 3023) was connected to the definitive electrode lead via a connecting cable (Interstim model 3095). The smaller type (Interstim model 3058) was connected directly to the definitive lead.

Loss of efficacy

Loss of efficacy was defined as a reduced effect or loss of therapeutic effect after implantation of the IPG after a period with good effect. Loss of efficacy was treated according to the algorithm of Dudding *et al.* [22]. In short, the electrode and pulse generator were first checked for technical failure. A technical check of the SNM system was always accompanied by a plain radiograph of the sacrum to exclude displacement of the electrode. Electrode polarity was changed if patients suffered from loss of efficacy. If changing polarity did not improve treatment efficacy, the second option was to increase the stimulation frequency to 21 or 31 Hz. A stimulation frequency of 31 Hz has only been applied recently [23,24].

In case of technical failure, a new electrode was implanted in the same sacral foramen. A contralateral electrode was implanted in case of clinical failure (loss of efficacy without technical failure).

Outcomes and follow-up

The primary outcome was defined as a defaecation frequency of three or more times per week without the use of additional laxatives. Secondary outcomes were change in straining frequency, abdominal pain and sensation of incomplete evacuation as assessed by the defaecation diary. Constipation severity was quantified by the CCCS and QoL using the Short-Form 36 (SF-36).

The SF-36 is a generic QoL questionnaire that consists of eight sub-domains: bodily pain (BP), general health (GH), social functioning (SF), physical functioning (PF), mental health, vitality (V), functioning physical role and functioning emotional role. All scales range

from 0 to 100, with a higher score indicating better QoL [25].

Both primary and secondary outcomes including CCCS were assessed at baseline, after the screening-period and at 1, 3, 6 and 12 months following permanent implantation and annually afterwards in both children and adults. Anorectal manometry and defaecography were not repeated during follow-up.

Additionally, both children and adults with a permanent stimulator *in situ* in December 2015 were asked to complete the SF-36 for a cross-sectional evaluation of QoL. If the questionnaires were not returned after 2 weeks, the patients were contacted by telephone and the questionnaires were sent again.

Complaints of pain related to the position of the IPG after implantation were observed for a minimum of 3 months. If the pain remained, patients were eligible for a revision of the pocket. In the early period of SNM, pain was treated by a relocation of the pulse generator to the lower abdominal wall or even the subpectoral space. Later, relocation of the pulse generator more caudal or cranial within the buttocks was preferred over relocation to the abdominal wall.

Wound infections were first aggressively treated with oral antibiotics. If this did not resolve the infection, the complete SNM system was removed. A new SNM system was implanted 3 months after the infection resolved.

Statistical analysis

Data are presented as mean (SD) or median (range) for continuous variables and count (percentage) for categorical variables. We used paired *t*-tests to compare follow-up results with baseline data. To compare outcomes between children and adults we used the Pearson's chi-square test for dichotomous variables and independent *t*-tests for continuous variables. Results of the SF-36 questionnaire were compared with the Dutch population using a one-sample *t*-test. Long-term efficacy was evaluated as the proportion of successfully implanted patients at the follow-up evaluations compared with the total number of patients undergoing SNM-screening. This analysis was performed for the whole population and for both groups. Primary and secondary outcomes and SF-36 questionnaires were evaluated using only the proportion of the number of patients of both groups who actually received a permanent implant. Patients who failed SNM screening were not included in these analyses due to missing data. Statistical significance was defined as $P < 0.05$. Data were analysed using SPSS (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp, Armonk, New York, USA).

Results

During the study period, 180 patients were eligible for SNM screening (45 children, 135 adults). Patient characteristics are shown in Table 1. Significantly more children had a defaecation frequency of three or more times per week after the SNM screening (84.4% of all screened children) compared with adults (65.2% of all screened adults) ($P = 0.005$).

In total, 201 test periods were conducted and 126 patients (38 children, 88 adults) received permanent SNM (1 S2 right, 56 S3 right, 62 S3 left, 2 S4 right, 5 S4 left). There was no difference in long-term outcomes between the different sacral foramina. In total, 82 patients (45.6% of all screened patients; 65.1% of all patients who received a permanent implant) maintained a defaecation frequency of three or more times per week. Mean follow-up was 47.5 (4.5–112.4) months in children and 47.3 (3.0–146.6) months in adults (Fig. 1).

Primary outcome

Children's defaecation frequency per 3 weeks increased from 5.6 (SD 13.3) (or 1.7 times per week) at baseline to 16.6 (SD 9.5) (or 5.5 times per week) after SNM ($P < 0.001$). Adult defaecation frequency per 3 weeks increased from 6.7 (SD 11.5) (or 2.2 times per week) at baseline to 9.9 (SD 15.3) (or 3.3 times per week) after SNM ($P < 0.001$). This effect remained significant in both the children and adults up to 48 months follow-up ($P < 0.001$ and $P = 0.03$, respectively) (Fig. 2). Defaecation frequency at baseline ($P = 0.55$) and after the test-phase ($P = 0.094$) did not differ significantly between children and adults. From 1-month follow-up

up to 5 years of follow-up, the defaecation frequency in adults (34.3, SD 7.3) was higher than in children (14.0, SD 7.8) ($P = 0.017$). After SNM, use of additional laxatives and/or enemas for regular bowel movements was comparable between children ($n = 14$; 36.8% of all patients who received a permanent implant) and adults ($n = 39$; 44.3% of all patients who received a permanent implant) ($P = 0.55$).

Secondary outcomes

The number of days with abdominal pain per 3 weeks at baseline decreased from 15.5 (SD 9.6) to 8.4 (SD 8.2) in children ($P = 0.014$) and from 18.2 (SD 6.7) to 9.2 (SD 6.4) in adults after SNM ($P < 0.001$). The frequency of abdominal pain remained lower compared with baseline in children up to 12 months of follow-up ($P = 0.01$) and in adults up to 24 months ($P = 0.022$). There was no significant difference in the number of episodes of abdominal pain during follow up between children and adults (Fig. 3).

Additional symptoms such as straining frequency and number of bowel actions with sensation of incomplete evacuation showed a comparable, but nonsignificant, decrease in both children and adults.

Cleveland Clinic Constipation Score

In children, the mean CCCS decreased from 17.9 (SD 4) at baseline to 8.9 (SD 4.2) after SNM ($P < 0.001$). For adults the CCCS was 17.3 (SD 3.5) at baseline *vs* 8.3 (SD 4.1) after SNM ($P < 0.001$). The decreased CCCS was maintained up to 5 years of follow-up in children ($P = 0.004$) and up to 36 months in adults ($P = 0.046$). There were no significant differences in

Table 1 Patient characteristics.

	Children ($n = 45$)	Adults ($n = 135$)	<i>P</i> -value
Male gender, n (%)	3 (6.7%)	12 (8.9%)	< 0.001
Mean age (years) (range)	15.8 (10.4–17.9)	41.4 (18.0–78.6)	< 0.001
SNM screening, n (%)			
Success	38 (84.4%)	88 (65.2%)	0.005
Failed	37 (15.6%)	47 (34.8%)	
Mean follow-up (months) (range)	47.5 (4.5–112.4)	47.3 (3.0–146.6)	0.97
Type of electrode			
Fixed electrode	30	18	0.001
Tined lead	38	70	0.001
Type of IPG			
Interstim I (3023)	34	40	< 0.001
Interstim II (3058)	34	48	< 0.001

SNM, sacral neuromodulation; IPG, implantable pulse generator.

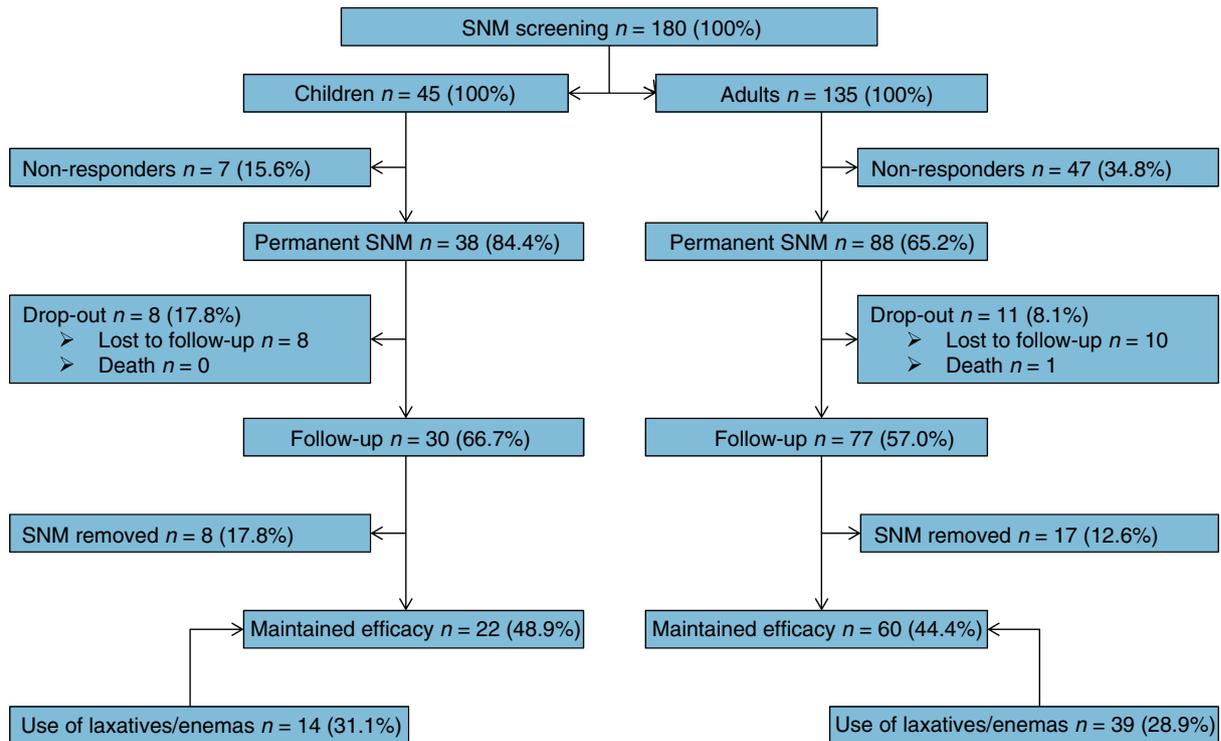


Figure 1 Flow-chart of long-term results regarding maintained efficacy subdivided between children and adults.

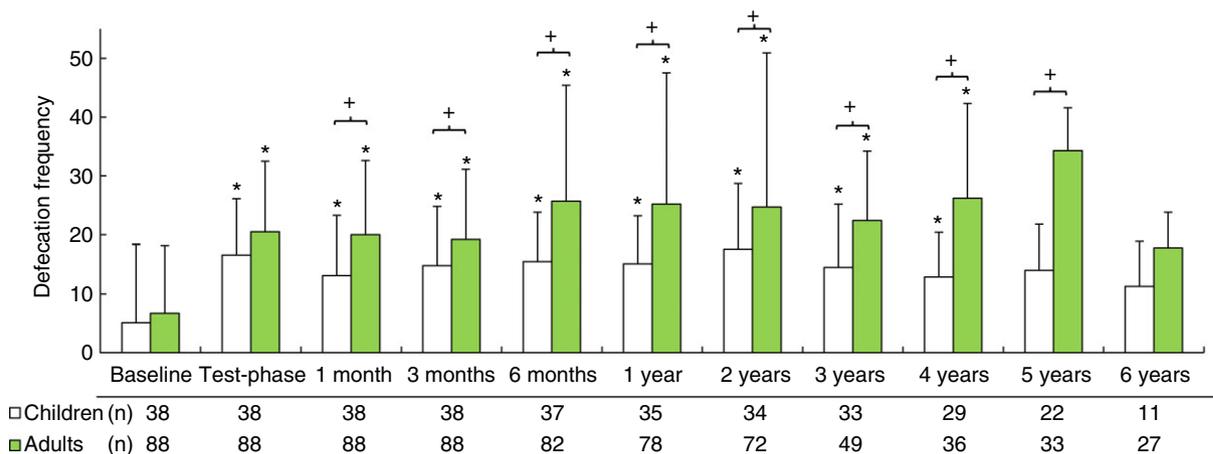


Figure 2 Number of successful defaecations per 3 weeks. Numbers beneath the graph represent the number of patients at each follow-up moment. *Significantly different compared with baseline. + Significantly different between children and adults.

CCCS between children and adults during follow-up (Fig. 4).

Short-Form 36

Ten of the 22 children and 36 of the 60 adults still receiving SNM returned the SF-36, resulting in an overall response-rate of 56.1%. Follow-up varied between 6 months and 12.1 years in children and

between 6 months and 11.1 years in adults. Children scored worse on BP (45.5, SD 23.2), GH (50.4, SD 22.4) and V (42, SD 20.6) compared with the Dutch population [BP 74.9, SD 23.4 ($P = 0.003$); GH 70.7, SD 20.7 ($P = 0.019$); V 68.6, SD 19.3 ($P = 0.003$)] (Fig. 5) [26]. Adults had impaired scores on PF (70.5, SD 27.8), BP (41.9, SD 24.5), GH (50.7, SD 23.2), V (55.3, SD 21.5) and SF (69.8, SD 28.6) compared with the Dutch population [PF 83, SD 17 ($P = 0.011$); BP

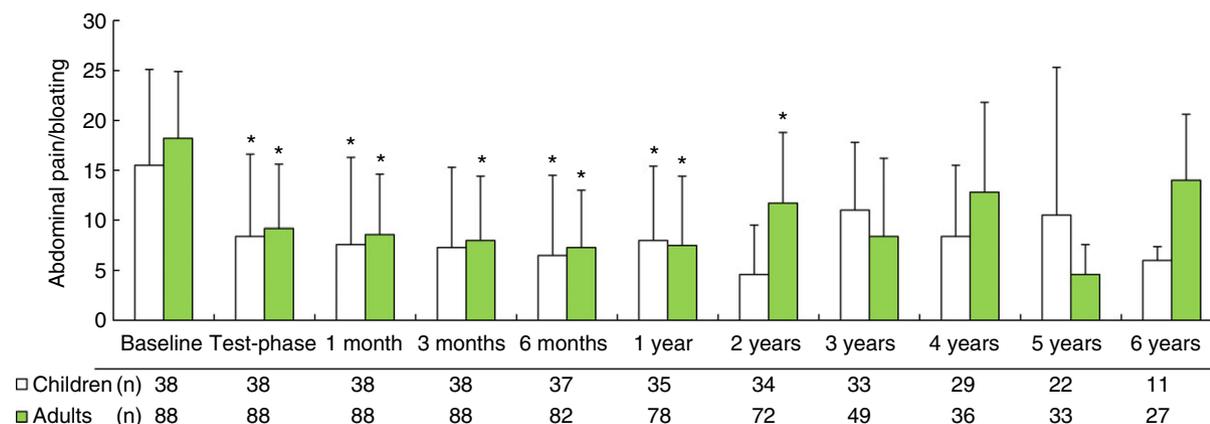


Figure 3 Number of days with abdominal pain or bloating per 3 weeks. Numbers beneath the graph represent the number of patients at each follow-up moment. *Significantly different compared with baseline.

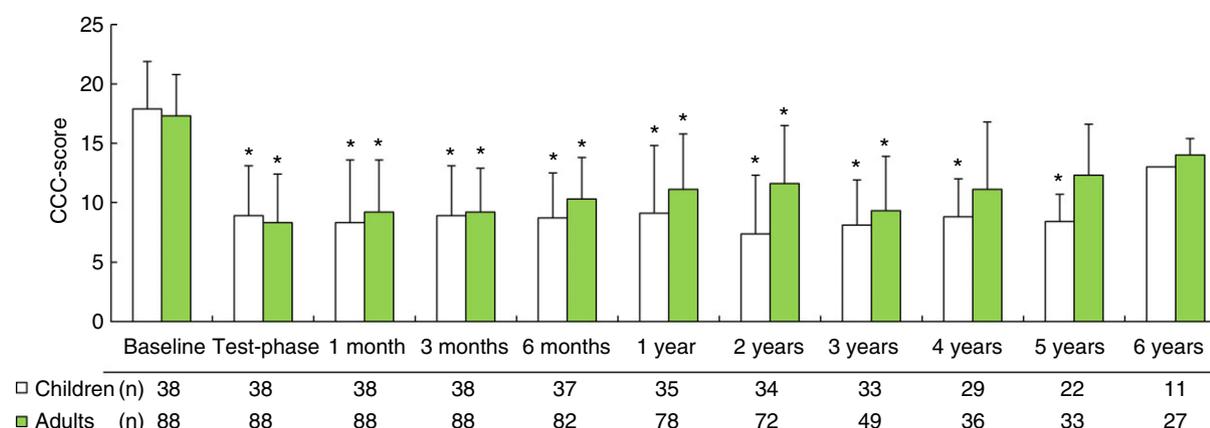


Figure 4 Cleveland Clinic Constipation Score during follow-up. Numbers beneath the graph represent the number of patients at each follow-up moment. *Significantly different compared with baseline.

74.9, SD 23.4 ($P < 0.001$); GH 70.7, SD 20.7 ($P < 0.001$); V 68.6, SD 19.3 ($P < 0.001$); SF 84, SD 15.3 ($P = 0.005$)]. Outcomes of the SF-36 showed no differences between children and adults.

Loss of efficacy

A total of 60 patients [18 children (40.0% of all screened children; 47.4% of all children who received a permanent implant) and 42 adults (31.1% of all screened adults; 47.7% of all adults who received a permanent implant)] suffered from loss of efficacy which required surgical intervention. Loss of efficacy in adults occurred in 18 of the 18 fixed leads (100%) and in 24 of the 70 tined leads (34.3%). Loss of efficacy occurred more in patients with a fixed lead compared with a tined lead ($P < 0.001$).

In 12 patients loss of efficacy was due to failure of the electrode, these patients received a new electrode. Efficacy was restored in seven patients after lead-

revision. Five patients suffered from subsequent clinical loss of efficacy for which they received a contralateral electrode. The percentages of patients suffering loss of efficacy were not significantly different between children and adults ($P = 0.97$).

Sacral neuromodulation (SNM) failed and was removed in 25 patients (8 children, 17 adults). Time between implantation of the permanent implant and date of removal of SNM was 2.4 (0.7–4.6) years for children and 2.4 (0.2–7.0) years for adults ($P = 0.97$). The number of patients in whom SNM was removed did not differ significantly between children and adults ($P = 0.82$).

Other adverse events

Pain or discomfort which required surgical intervention occurred in 27 patients [5 children (11.1% of all screened children; 13.2% of all children who received a permanent implant) and 22 adults (16.3% of all

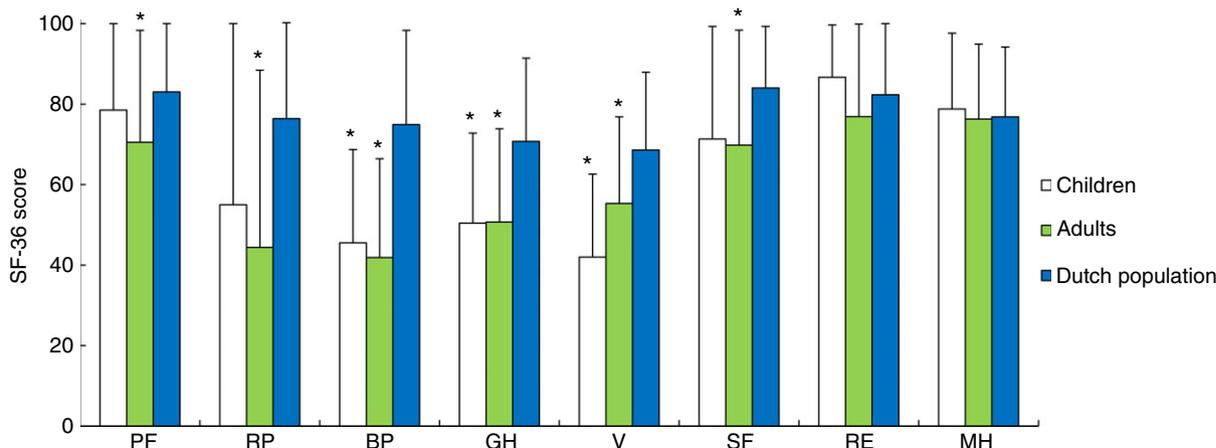


Figure 5 Outcome of the Short-Form-36 questionnaire (PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; V, vitality; SF, social functioning; RE, role emotional; MH, mental health). Values are given as mean (SD). *Significantly different compared with the Dutch population.

screened adults; 25.0% of all adults who received a permanent implant). This resulted in 11 surgical procedures in children and 27 surgical procedures in adults. In children, the IPG was relocated seven times within the gluteal region and once from the gluteal region to the abdominal region. In adults, the IPG was relocated 20 times within the gluteal region, four times from the gluteal region to the abdominal region and three times from the gluteal region directly to the subpectoral space.

An infection occurred in one child (2.6% of all children with a permanent implant) and in two adults (2.3% of all adults with a permanent implant). All were successfully treated with antibiotics.

Discussion

This study showed that SNM had an equally long-term beneficial effect on defaecation frequency in children (48.9%) and adults (44.4%) with intractable FC. Furthermore, both children and adults had less frequent abdominal pain and less constipation as assessed by the CCCS. QoL after SNM did not differ between children and adults. Loss of efficacy occurred in 40.0% and 31.1% of all screened children and adults, respectively.

Scarce data are available regarding the long-term outcome of SNM for FC in children and adults [9–11,13–16,27]. The sample size of these studies is often small (4–62 patients) and efficacy is often reported based on an analysis of the patients who received a permanent implant only instead of an analysis of the entire cohort of patients including all SNM-screenings.

Based on an analysis of the entire cohort of patients, previous studies reported a clinical efficacy of 49.0%–61.3% in both children and adults which is comparable to our results [9–11,14,27,28]. One study reported a clinical efficacy of 92% in children after a mean follow-up of 6 months [13]. In contrast, a lower clinical efficacy of SNM of 27.3%–29.0% has also been reported [15–17].

The efficacy of SNM for FC remains controversial as only a few studies with a high level of evidence are available. One sham-controlled study by Dinning *et al.* [17] reported a success-rate of 30% in 59 adult patients with slow-transit constipation after a 3-week period of SNM. Long-term success-rates in these patients were 18.9% ($n = 10$) at 1-year follow-up and 5.7% ($n = 3$) at 2-year follow-up [29]. A recent double-blind, sham-controlled randomized controlled trial (RCT) by Zerbib *et al.* [30] reported comparable results as they found no difference between subsensory stimulation and no stimulation.

There are several reasons for the large variety in outcome. Firstly, the heterogeneity of symptoms between patients may be important. It is reported that patients with more severe symptoms show less improvement than patients with milder symptoms [14,31,32]. Secondly, the variation in outcome may also be explained by the use of different outcome parameters, i.e. a defaecation frequency of two [13,27] or three times per week [10,14]. Finally, the aetiology of FC (i.e. slow transit constipation, pelvic outlet obstruction) may also influence the variation in outcome [15–17].

Surprisingly, in our study we found a higher defaecation frequency in adults than children during follow-up.

To our knowledge, this is the first study to compare the long-term outcomes of SNM for constipation between children and adults. Therefore it is difficult to distinguish between an incidental finding or a substantial difference between the two groups. These results could be biased due to the small number of patients per group. We cannot explain this difference from an anatomical or physiological point of view.

The general understanding of the mechanism of action of SNM for constipation is poor. Multiple studies have reported a decreased colon transit time and/or an increase in colon propulsion waves after implantation of SNM in patients suffering from slow-transit constipation [10,33,34]. However, these results could not be replicated by other studies [16,28,35]. A recent review evaluated the motor and sensory effects of SNM on the small intestine, colon and rectum and the effect of SNM on the central nervous system [36]. The authors hypothesized that SNM modulates the central defaecation control. However, more research is required to better understand the underlying mechanisms of action of SNM.

Cross-sectional evaluation showed a reduced QoL in both children and adults after SNM compared with the Dutch population regarding BP, GH and V. Adults also had an impaired score on SF. QoL did not differ between children and adults. A previous study by Kamm *et al.* [10] reported an improvement in QoL in patients with constipation after SNM compared with baseline. Interpretation of our results and a comparison with previous studies might be biased due to the absence of a baseline measurement and the cross-sectional evaluation in our study.

The most common adverse event in this study was loss of efficacy. Eighteen children and 42 adults experienced loss of efficacy requiring surgical intervention. Due to the retrospective nature of this study we could not differentiate between lack of efficacy and loss of efficacy. Only a few studies have reported the number of patients suffering from loss of efficacy after SNM for constipation. Our results are comparable to a previous study by Maeda *et al.*, [37] which reported a loss of efficacy of 45%. The underlying reasons for waning of efficacy remain unknown. It may be related to the possibility that prolonged stimulation may induce nerve injury, but it may also be related to aging of the patient with concomitant natural physical decline [37].

Most notable was the high failure rate of the fixed leads. There are no studies in the field of SNM for constipation reporting the success rates of the different leads. Therefore we compared our results with the limited results reported in the field of SNM for faecal

incontinence. As in our study, these previous studies all reported superiority of the tined lead compared with the fixed lead [38,39]. However, these results are difficult to compare because the number of patients in our study and in the literature are limited. We hypothesize that the high failure rate could be related to the technical difference between the fixed and tined leads. However, suboptimal patient selection may also play a substantial role. Due to the retrospective design of this study we could not differentiate between the causes of failure of SNM.

The strengths of this study are the large patient population, the comparison between children and adults and the use of validated questionnaires. However, there are also some limitations that need to be addressed. Firstly, this study included a heterogeneous group of patients, including patients with slow transit constipation and pelvic outlet obstruction. Secondly, different defaecation diaries were used during follow-up and the early versions mainly focused on defaecation frequency. This resulted in missing baseline values regarding secondary outcomes. Furthermore, we used a cross-sectional approach to assess general QoL (SF-36) due to the absence of baseline and follow-up data. These results must be interpreted with care as bias cannot be excluded due to the cross-sectional approach and low response-rate (56.1%) of this study. It is possible that patients with a lower QoL did not return the questionnaires, resulting in a false-positive outcome. Finally, data after 72 months of follow-up were not reported in this study due to the small sample size and the number of missing data.

In summary, this study demonstrates that SNM has similar long-term outcome for children (< 18 years) and adults with intractable FC. Therefore, in our opinion children suffering from severe constipation should be eligible for SNM screening.

It remains debatable whether this expensive treatment is a valid option for intractable FC as only half of all screened patients showed positive effects. Moreover, loss of efficacy occurred in roughly half of all patients who received permanent SNM. These outcomes should be included in the decision-making process regarding the treatment paradigm between the healthcare provider and the patient with intractable FC. The options are continuing care as usual, SNM or more invasive therapies like subtotal colectomy.

There is a RCT currently under way in the Netherlands regarding the (cost-) effectiveness of SNM for constipation in children and adults, comparing SNM with optimal conservative treatment (ClinicalTrials.gov no. NCT02961582). This should provide improved information to help decision-making for both patients and their doctors.

Author contributions

PJ, MB, LS, NB, JM and SB designed the study; PJ and YM performed the research; PJ, YM, AR, JM and SB analysed and interpreted the data; PJ, AR, MB, LS, NB, SB and JM drafted the manuscript; MB, LS, NB, JM and SB supervised the study. All authors gave final approval of the final version.

Conflicts of interest

PJ, JM and SB received a nonrestrictive grant from Medtronic for research. MB is a consultant for Shire, Sucampo, Norgine, Coloplast, Danone, Frieslandcampina, Sensus and Novalac. YM, SK, LS and NB have no conflicts of interest.

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