### Title

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# Sacral Nerve Stimulation Allows for Decreased Antegrade Continence Enema Use in Children with Intractable Constipation

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**ABSTRACT**

**Background:** Sacral nerve stimulation (SNS) can be beneficial for children with constipation, but no studies have focused on children with constipation severe enough to require antegrade continence enemas (ACE). Our objective was to evaluate the efficacy of SNS in children with constipation treated with ACE.

**Methods:** Using a prospective patient registry, we identified patients <21 years old who were receiving ACE prior to SNS placement. We compared ACE/laxative usage, PedsQL Gastrointestinal Symptom Scale (GSS), Fecal Incontinence Quality of Life Scale (FIQL), Fecal Incontinence Severity Index (FISI), and Vancouver Dysfunctional Elimination Syndrome Score (DES) at baseline and progressive follow-up time intervals.

**Results:** Twenty-two subjects (55% male, median 12 years) were included. Median ACE frequency decreased from 7 per week at baseline to 1 per week at 12 months ($p<0.0001$). Ten children (45%) had their cecostomy/appendicostomy closed. Laxative use, GSS, FIQL, and DES did not change. FISI improved over the first 12 months with statistical significance reached only at 6 months ($p=0.02$). Six (27%) children experienced complications after SNS that required further surgery.

**Conclusions:** In children with intractable constipation dependent on ACE, SNS led to a steady decrease in ACE usage with nearly half of subjects receiving cecostomy/ appendicostomy closure within 2 years.

**Key Words:** Electrical Stimulation; Neuromodulation; Cecostomy; Appendicostomy; Fecal Incontinence

**Abbreviations:**

ACE, antegrade continence enema

SNS, sacral nerve stimulation

FI, fecal incontinence

GSS, PedsQL Gastrointestinal Symptom Scale

FIQL, Fecal Incontinence Quality of Life Scale

FISI, Fecal Incontinence Severity Index

DES, Vancouver Dysfunctional Elimination Syndrome Score

ARM, anorectal malformation

## INTRODUCTION

Constipation is a common childhood medical problem with an estimated worldwide prevalence of 12% [1]. Conventional treatment options for pediatric constipation consist of behavioral modification and medications, including osmotic and stimulant laxatives [2]. Despite intensive conventional treatment, 40% of children with constipation evaluated in a specialty clinic are not successfully treated at 1 year [3]. Intractable constipation is defined as constipation that persists despite at least 3 months of optimal conventional treatment [2]. Treatment options for children with intractable constipation are limited. Antegrade continence enema (ACE) administration has become an established treatment for children with intractable constipation and can lead to improvement in both symptom severity and quality of life [4, 5]. However, studies show that up to 31% of children do not respond adequately to ACE [6].

Sacral nerve stimulation (SNS) involves long-term direct electrical stimulation of the sacral nerve root by an implanted lead connected to a pulse generator. SNS has been shown to be beneficial for adults with constipation and fecal incontinence (FI) [7, 8]. Although evidence remains limited, recent studies in children suggest that SNS may be effective for children with constipation and FI as well [9, 10]. However, no studies have focused on children with constipation severe enough to require ACE. The objective of our study was to evaluate the efficacy of SNS in children with intractable constipation dependent on ACE.

## 1. METHODS

We performed a prospective observational cohort study. We included patients up to 21 years of age treated with ACE for intractable constipation who

underwent SNS implantation at our institution between 2012 and 2014. ACE usage, laxative usage, patient-reported outcomes, and complications of SNS were recorded at baseline and at each follow-up visit. Patient-reported measures of symptom severity and quality of life included the PedsQL Gastrointestinal Symptom Scale (GSS), Fecal Incontinence Quality of Life Scale (FIQL), Fecal Incontinence Severity Index (FISI), and Vancouver Dysfunctional Elimination Syndrome Score (DES) [11-14]. This information was entered into a patient registry using the REDCap© electronic data capture tool [15]. Charts were reviewed to verify medication and ACE usage, diagnostic test results, and to gather details of related complications. Our study protocol was approved by the Institutional Review Board.

*1.1 Sacral Nerve Stimulation Procedure*

All patients had SNS therapy initiated in two stages [10, 16]. Both procedures were performed with the patient under general anesthesia and in the prone position. The first stage involved insertion of a tined lead at the S3 sacral nerve root under fluoroscopic guidance. The InterStim® System (Medtronic, Inc., Minneapolis, MN) lead was then inserted using the Seldinger technique. This lead was connected to a temporary stimulator and positioning confirmed by observing for a bellows response of the pelvic floor and great toe plantar flexion with stimulation. Symptoms were then monitored closely for the next two weeks with the temporary stimulator in place. If clinical improvement was observed, the patient proceeded to the second stage, which involved connecting the previously inserted lead to a permanent stimulator and implantation of this stimulator within the subcutaneous tissue of the buttock.

*1.2 Data Collection and Analysis*

Using the patient registry, we selected encounters at baseline and 1, 3, 6, 9, 12, 18 and 24 months after SNS implantation (+/-30 days for 1, 3, 6, 9, and 12 months and +/-60 days for 18 and 24 months). We compared ACE usage, laxative usage, GSS, FIQL, FISI, and DES at baseline to each follow-up encounter. We also compared subgroups divided by gender and presence of anorectal malformation (ARM), FI, and urinary symptoms. We did not compare GSS, FIQL, FISI, or DES between subgroups divided based on the presence of FI or urinary symptoms, as the presence of FI or urinary symptoms would inherently lead to differences in these scores. Wilcoxon rank sum tests were used for comparison and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC).

## 2. RESULTS

*2.1 Subject Characteristics*

Twenty-two participants (55% male, median age 12 years at SNS initiation, range 6-19) were included. The median follow-up time was 18 months. Eleven patients (50%) had a history of ARM, 6 (27%) had a history of tethered spinal cord, and 1 (5%) had Hirschsprung disease. The remaining 10 (45%) were classified as having functional constipation. Thirteen patients (59%) had FI and 14 (64%) had urinary symptoms.

*2.2 ACE and Laxative Usage*

Of the 22 participants, 12 (55%) had a cecostomy and 10 (45%) had an appendicostomy. The cecostomy or appendicostomy had been in place for a

median of 4.5 years prior to SNS initiation. Cleansing solutions varied in both volume and composition, but generally included either normal saline or a polyethylene glycol and electrolyte solution. Fifteen participants (68%) were using cleansing solutions that also contained a stimulant laxative, generally bisacodyl or glycerin.

As shown in **Figure 1**, the cohort reported decreasing ACE usage across the study period. Prior to SNS, patients received a median of 7 (IQR 7-7) ACE per week. Beginning at 3 months after SNS initiation, ACE frequency steadily decreased and reached 1 (IQR 0-4) per week at 12 months ($p<0.0001$). Over the course of the study, 10 participants (45%) had their cecostomy or appendicostomy electively closed, the majority (80%) of which were closed within 12 months (**Figure 2**). There was no change in oral laxative use over time. We were unable to detect any significant differences in the decrease of ACE usage over time based on gender, history of ARM, presence of fecal incontinence, or presence of urinary symptoms (**Figure 3**).

*2.3 Patient-Reported Outcomes*

**Figure 4** shows the four patient-reported measures of symptom severity and quality of life at baseline and after SNS initiation. GSS and DES scores did not change significantly over the study period. All four components of the FIQL showed a non-significant improvement after SNS. FISI improved over the first 12 months after SNS and reached significance only at 6 months ($p=0.021$).

*2.4 Complications*

Six patients (27%) experienced complications after SNS implantation that required further surgery. Four required SNS removal for wound infection. One required removal for lead displacement that was unable to be replaced. A sixth participant experienced lower extremity numbness and discomfort when sitting that resolved with repositioning of the stimulator. Three of the 4 patients who experienced wound infection underwent SNS replacement after treatment, but 1 participant developed a second wound infection requiring a second SNS removal.

## 3. DISCUSSION

This study demonstrates that children with intractable constipation who require ACE administration can be successfully treated with SNS. Patients showed a steady decrease in ACE usage over the first year after SNS initiation with nearly half of patients undergoing appendicostomy or cecostomy closure. Patient-reported measures of symptom severity and quality of life with regards to the fecal incontinence improved non-significantly after SNS placement.

Evidence-based guidelines on the evaluation and treatment of functional constipation in children published by the European and North American societies for pediatric gastroenterology include SNS as a treatment option for children with intractable constipation, along with ACE and partial or total colonic resection [2]. Both SNS and ACE are treatments that are generally reversible, which is particularly relevant to the pediatric population. In adults with constipation and FI, SNS has been used to bridge the gap between conventional medical treatment and more invasive surgical procedures directly involving the bowel [8, 17]. The role of SNS in the management of children with intractable constipation, however, is less well defined.

Interpretation of the findings of this study requires an understanding of what is known regarding the outcomes of ACE treatment in children with intractable constipation. A recent review by Kuizenga-Wessel and colleagues showed that the available literature on the use of ACE in children has been variable in both the definition of treatment success and rate of success [18]. A survey of pediatric gastroenterologists and surgeons who regularly prescribe ACE regimens showed differences in preoperative evaluation, cleansing solutions, and willingness to wean ACE treatment, all factors that could lead to heterogeneity in rates of success [18].

Despite this uncertainty, it is clear that in this study, children with intractable constipation were able to decrease and ultimately discontinue ACE usage to a greater extent than what has been reported in the literature for children treated with ACE alone. Mugie and colleagues previously described our institutional experience with 99 children treated with ACE and found that 13% had improved to the point of discontinuing ACE use at a median of 46 months after ACE initiation [4]. Siddiqui and colleagues reported that of 117 children treated with ACE, only 6% had improved to the point of discontinuing ACE use at a mean of 68 months [6]. Randall and colleagues reported that of 203 children treated with ACE, 26% had discontinued ACE use and 16% had undergone closure of cecostomy or appendicostomy at a mean of 68 months [19]. Our results show higher rates of both discontinuation of ACE and closure of cecostomy or appendicostomy after initiation of SNS treatment.

As experience with long-term use of ACE in children grows, investigators have begun to describe decreasing rates of success with longer follow-up duration after starting ACE treatment [20]. In a cohort of children treated with ACE in England, Dey and colleagues initially reported that 18% had discontinued ACE use after a

median follow-up duration of 5.4 years, primarily because of ineffectiveness and complications. In a subsequent study of the same cohort, Yardley and colleagues reported that 41% were no longer using ACE after 11 years, not because of symptomatic improvement but rather decreased effectiveness, complications, psychological factors, and non-compliance [21]. SNS may be an appropriate treatment option for the subset of children with intractable constipation who no longer respond to ACE.

It remains unclear whether our subjects were able to decrease ACE use because SNS treatment independently led to improvement in constipation or because SNS affected how subjects responded to ACE treatment. During the course of our study, some subjects described an improvement in their response to ACE after SNS initiation, including a decrease in the time from ACE administration to defecation and a stronger urge to defecate after ACE. We did not measure these changes as part of this study and cannot draw any conclusions from these descriptions other than to encourage further investigation. However, these reports may be consistent with our limited understanding of the effects of SNS on defecatory mechanisms.

The mechanism of SNS in the treatment of constipation and FI remains incompletely understood. It is likely that SNS acts on abnormalities in physiological control of defecation common to both constipation and FI [22]. There is evidence that SNS modulates colonic motility and can increase the frequency of colonic propagating contractions in adults with slow-transit constipation [22, 23]. The presence of colonic high-amplitude propagating contractions in children with constipation is associated with improved response to ACE [24]. Improvement in colonic motility with SNS could therefore decrease the length of time from ACE

administration to defecation. There is also evidence that SNS increases rectal sensitivity as measured by rectal barostat test or anorectal manometry [22, 25]. If SNS increases rectal sensitivity, it would decrease the threshold of rectal distention at which the urge to defecate is experienced and could lead to a stronger urge to defecate after ACE administration.

This study has several limitations. First, the size of our cohort was limited, a factor that decreased our ability to detect statistically significant changes at the specified time points and prevented subgroup analyses. Second, our cohort was heterogeneous in that it included children with both functional and organic causes of constipation. We attempted to evaluate for differences in SNS response based on gender, history of ARM, presence of fecal incontinence, or presence of urinary symptoms. Our data suggests that patients with a history of ARM and those without urinary symptoms may be able to decrease ACE usage earlier and to a larger degree than those without an ARM diagnosis or those with urinary symptoms respectively, but this was unable to be statistically evaluated as subgroups due to small sample size. Third, because we selected follow-up encounters within predetermined time intervals, patients often did not have encounters at each time point, particularly at longer lengths of time from SNS initiation. This made our outcome measures at those time points more susceptible to variation. Finally, the possibility remains that subjects were able to decrease ACE usage in part because of more frequent follow-up after SNS initiation. Further research comparing the two treatment options is needed, not only to evaluate effects on symptoms and quality of life but also to assess the burden associated with each treatment.

In conclusion, SNS is a promising therapy for children with intractable constipation dependent on ACE and may lead to decreased need for ACE and

improvement in quality of life. Treatment options for children with constipation refractory to conventional treatment are limited, and further studies are needed to better define the role of SNS in the management of these children. We propose that SNS treatment warrants consideration in the management of children with intractable constipation who are dependent on ACE or inadequately treated with ACE, particularly if the child has already been treated with ACE for a number of years.

**REFERENCES**


1. Mugie SM, Benninga MA, Di Lorenzo C: Epidemiology of constipation in children and adults: a systematic review. Best practice & research Clinical gastroenterology 25:3-18, 2011
2. Tabbers MM, DiLorenzo C, Berger MY, et al: Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. Journal of pediatric gastroenterology and nutrition 58:258-274, 2014
3. van Ginkel R, Reitsma JB, Buller HA, et al: Childhood constipation: longitudinal follow-up beyond puberty. Gastroenterology 125:357-363, 2003
4. Mugie SM, Machado RS, Mousa HM, et al: Ten-year experience using antegrade enemas in children. The Journal of pediatrics 161:700-704, 2012
5. Har AF, Rescorla FJ, Croffie JM: Quality of life in pediatric patients with unremitting constipation pre and post Malone Antegrade Continence Enema (MACE) procedure. Journal of pediatric surgery 48:1733-1737, 2013
6. Siddiqui AA, Fishman SJ, Bauer SB, et al: Long-term follow-up of patients after antegrade continence enema procedure. Journal of pediatric gastroenterology and nutrition 52:574-580, 2011
7. Kamm MA, Dudding TC, Melenhorst J, et al: Sacral nerve stimulation for intractable constipation. Gut 59:333-340, 2010
8. Thomas GP, Dudding TC, Rahbour G, et al: Sacral nerve stimulation for constipation. The British journal of surgery 100:174-181, 2013
9. van Wunnik BP, Peeters B, Govaert B, et al: Sacral neuromodulation therapy: a promising treatment for adolescents with refractory functional constipation. Diseases of the colon and rectum 55:278-285, 2012
10. Sulkowski JP, Nacion KM, Deans KJ, et al: Sacral nerve stimulation: a promising therapy for fecal and urinary incontinence and constipation in children. Journal of pediatric surgery 50:1644-1647, 2015
11. Varni JW, Lane MM, Burwinkle TM, et al: Health-related quality of life in pediatric patients with irritable bowel syndrome: a comparative analysis. Journal of developmental and behavioral pediatrics : JDBP 27:451-458, 2006
12. Rockwood TH, Church JM, Fleshman JW, et al: Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. Diseases of the colon and rectum 43:9-16; discussion 16-17, 2000
13. Rockwood TH, Church JM, Fleshman JW, et al: Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. Diseases of the colon and rectum 42:1525-1532, 1999
14. Afshar K, Mirbagheri A, Scott H, et al: Development of a symptom score for dysfunctional elimination syndrome. The Journal of urology 182:1939-1943, 2009
15. Harris PA, Taylor R, Thielke R, et al: Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics 42:377-381, 2009
16. Schober MS, Sulkowski JP, Lu PL, et al: Sacral Nerve Stimulation for Pediatric Lower Urinary Tract Dysfunction: Development of a Standardized Pathway

with Objective Urodynamic Outcomes. The Journal of urology 194:1721-1727, 2015
17. Thaha MA, Abukar AA, Thin NN, et al: Sacral nerve stimulation for faecal incontinence and constipation in adults. The Cochrane database of systematic reviews 8:CD004464, 2015
18. Kuizenga-Wessel S, Mousa HM, Benninga MA, et al: Lack of Agreement on How to Use Antegrade Enemas in Children. Journal of pediatric gastroenterology and nutrition 62:71-79, 2016
19. Randall J, Coyne P, Jaffray B: Follow up of children undergoing antegrade continent enema: experience of over two hundred cases. Journal of pediatric surgery 49:1405-1408, 2014
20. Rodriguez L, Nurko S, Flores A: Factors associated with successful decrease and discontinuation of antegrade continence enemas (ACE) in children with defecation disorders: a study evaluating the effect of ACE on colon motility. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society 25:140-e181, 2013
21. Yardley IE, Pauniaho SL, Baillie CT, et al: After the honeymoon comes divorce: long-term use of the antegrade continence enema procedure. Journal of pediatric surgery 44:1274-1276; discussion 1276-1277, 2009
22. Carrington EV, Evers J, Grossi U, et al: A systematic review of sacral nerve stimulation mechanisms in the treatment of fecal incontinence and constipation. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society 26:1222-1237, 2014
23. Dinning PG, Fuentealba SE, Kennedy ML, et al: Sacral nerve stimulation induces pan-colonic propagating pressure waves and increases defecation frequency in patients with slow-transit constipation. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland 9:123-132, 2007
24. van den Berg MM, Hogan M, Caniano DA, et al: Colonic manometry as predictor of cecostomy success in children with defecation disorders. Journal of pediatric surgery 41:730-736; discussion 730-736, 2006
25. Knowles CH, Thin N, Gill K, et al: Prospective randomized double-blind study of temporary sacral nerve stimulation in patients with rectal evacuatory dysfunction and rectal hyposensitivity. Annals of surgery 255:643-649, 2012

**FIGURE LEGENDS**

Figure 1: Number of antegrade continence enemas used per week at baseline and at follow-up in months.

**denotes statistical significance compared to baseline, p<0.05, ** p<0.01*

Figure 2: Number of subjects who have undergone cecostomy/appendicostomy closure at baseline and at follow-up in months.

Figure 3: Number of antegrade continence enemas used per week at baseline and at follow-up in months after stratification by (A) gender, (B) presence of anorectal malformation, (C) presence of fecal incontinence, and (D) presence of urinary symptoms.

*M, Male*

*F, Female*

Figure 4: Patient-reported outcomes at baseline and at follow-up in months. For the GSS and FIQL, higher scores suggest improvement. For the FISI and DES, lower scores suggest improvement.

*GSS, PedsQL Gastrointestinal Symptom Scale*

*FIQL, Fecal Incontinence Quality of Life Scale*

*FISI, Fecal Incontinence Severity Index*

*DES, Vancouver Dysfunctional Elimination Syndrome Score*