

Prospective Evaluation of Sacral Neuromodulation in Children: Outcomes and Urodynamic Predictors of Success

Matthew D. Mason,* Heidi A. Stephany, Daniel P. Casella, Douglass B. Clayton, Stacy T. Tanaka, John C. Thomas, Mark C. Adams, John W. Brock III and John C. Pope IV

From the Division of Pediatric Urology, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee, and Division of Pediatric Urology, Children's Hospital of Pittsburgh (HAS), Pittsburgh, Pennsylvania

Purpose: Sacral neuromodulation has been demonstrated to improve refractory bowel bladder dysfunction in children. The purpose of the current study was to determine whether results are durable in children after longer followup, whether children with a lower body mass index are at risk for device failure and whether pretreatment urodynamic evaluation can predict posttreatment outcome.

Materials and Methods: Pediatric patients with refractory bowel bladder dysfunction were enrolled following informed consent and followed prospectively. All patients underwent preoperative videourodynamic evaluation and a 2-stage implantation procedure. Validated questionnaires were used to assess symptom severity and quality of life. Complications were analyzed with regard to treatment required and patient body mass index.

Results: During 45 months 30 patients were enrolled. Median age was 8.3 years at enrollment. Median followup was 14.8 months. Patients had significant improvement in quality of life and symptom scores, which persisted at the most recent followup. Patients who had uninhibited detrusor contractions on preoperative urodynamic assessment had significantly greater improvement in symptoms. Of the patients 23% had a complication requiring reoperation, most commonly neurostimulator lead breakage in those with a significantly lower body mass index.

Conclusions: Sacral neuromodulation significantly improves quality of life and symptom severity in children with refractory bowel bladder dysfunction. Children gain greater benefit if they show uninhibited bladder contractions on preoperative urodynamic evaluation. Children have a high rate of lead breakage requiring operative revision, which was seen after minor trauma in those with a lower body mass index.

Key Words: urinary bladder, electric stimulation, lower urinary tract symptoms, quality of life, questionnaires

SACRAL neuromodulation is approved by the FDA for the treatment of urinary and fecal symptoms in adults. Many studies have demonstrated the efficacy of SNM in adults but few groups have investigated SNM in children. Studies of SNM in children with nonneurogenic BBD have shown

promising results with improvement in symptoms and subjective assessment of patient satisfaction but significantly high rates of reoperation estimated at 11% to 56%.¹⁻⁵

Our group has previously reported our results of SNM in children with refractory BBD using validated

Abbreviations and Acronyms

BBD = bowel bladder dysfunction
BMI = body mass index
FDA = Food and Drug Administration
MRI = magnetic resonance imaging
QOL = quality of life
SNM = sacral neuromodulation

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* Correspondence: Pediatric Urology, Upstate Medical University, 725 Irving Ave., Suite 406, Syracuse, New York 13210 (telephone: 315-464-6060; FAX: 315-464-5115; e-mail: masonm@upstate.edu).

questionnaires to assess the severity of BBD and patient QOL.⁶ The purpose of the current study was to determine whether SNM results are durable in children after longer followup, whether children with a lower BMI are at risk for device failure and whether pretreatment urodynamic evaluation can predict posttreatment outcome.

METHODS

Patient Population

After receiving approval from our institutional review board (No. 140834) we identified patients eligible for SNM. Inclusion criteria were age at least 5 years and BBD refractory to conservative measures, including behavioral and dietary modification, treatment of constipation, medical therapy (including anticholinergics or α -blockers) and pelvic floor rehabilitation with biofeedback when indicated. All patients underwent preoperative multi-channel videourodynamic evaluation. Spinal MRI was performed in any patient with concern of neurological etiology (coexisting significant bowel symptoms or lower extremity dysfunction). All patients were counseled that SNM treatment in children is still considered investigational and it is not FDA approved. All families participating in the study provided written informed consent and were followed prospectively. BMI calculations were performed using height and weight measurements recorded on the day of the stage 1 SNM procedure.

Operative Procedure

All patients underwent 2-stage implantation of an InterStim II® SNM device. At stage 1 patients under general anesthesia underwent placement of a tined quadripolar stimulator lead under fluoroscopic guidance. The bellows response and great toe flexion were observed to ensure appropriate unilateral stimulation of the S3 nerve. Patients were sent home the same day with an external pulse generator. After a 1-week trial period patients underwent placement of an implantable pulse generator if they reported improved symptoms, satisfaction with treatment and no significant side effects, and elected to proceed.

Outcome Assessment

We used 2 previously validated questionnaires, including the Vancouver NLUTD/DES (Nonneurogenic Lower Urinary Tract Dysfunction/Dysfunctional Elimination Syndrome) questionnaire to assess BBD severity and the PedsQL™ 4.0 generic core scales to assess QOL.^{7,8} The Vancouver NLUTD/DES questionnaire contains 14 Likert scale questions, each scored from 0 to 4. Ten questions address urinary symptoms, 3 address bowel symptoms and the final question addresses the ease of answering the questionnaire with the latter not included in the symptom score. A total score of 0 to 52 is possible, a score of at least 11 indicates BBD and higher scores indicate worse symptoms. The PedsQL questionnaire consists of 23 Likert scale questions, each scored from 0 to 4. The questions assess physical, emotional, social and school related elements of QOL. The questionnaire provides a physical

QOL score, a psychosocial QOL score and a total QOL score, each ranging from 0 to 100 with higher scores indicating better QOL. Patients completed these questionnaires before the stage 1 SNM procedure, 1 week after the stage 1 procedure and at every subsequent followup visit.

Medication use before and after SNM treatment was recorded as use or nonuse of daily antibiotic prophylaxis and use or nonuse of anticholinergics and/or α -blockers. Patients were not instructed to discontinue use of these medications at the time of SNM but rather were allowed to discontinue use after sufficient symptom improvement. Complications after SNM were analyzed with specific attention given to complications requiring operative intervention. BMI in patients with a complication related to device breakage was compared to BMI in the remainder of the cohort.

An estimate of the number of initial visits for BBD at our pediatric urology clinic during the study period was obtained by querying our institutional administrative billing database for ICD-9 codes, including 596.59 (other bladder dysfunction), 788.1 (dysuria), 788.21 (incomplete bladder emptying), 788.30 (urinary incontinence not otherwise specified), 788.36 (nocturnal enuresis), 788.41 (urinary frequency), 788.63 (urgency of urination), 788.31 (urge incontinence) and 788.64 (urinary hesitancy).

All data were managed using REDCap (Research Electronic Data Capture) tools hosted at our institution.⁹ REDCap is a secure, web based application designed to support data capture for research studies.

Statistical Analyses

Statistical analyses were performed using Prism® 6 for Windows®. Total questionnaire scores, domain questionnaire scores and individual question responses were compared preoperatively, after the stage 1 procedure and at followup using repeated measures 1-way ANOVA. Questionnaire score improvement in patient groups with or without specific urodynamic findings as well as the BMI of patient groups with or without specific complications were compared using the unpaired t-test and the Welch correction with $p < 0.05$ considered statistically significant.

RESULTS

From July 2011 to April 2015 approximately 8,000 new patients were seen for a BBD diagnosis at our pediatric urology clinic, of whom 24 females and 6 males were prospectively enrolled in the study during this time frame. Median age at study enrollment was 8.3 years (range 5.5 to 17.4, IQR 7.2–12.6). Patients had a median of 7 clinic visits during 27 months before proceeding to SNM. Spinal MRI was performed in 21 patients (70%) and revealed no relevant findings. No patients were excluded from study due to MRI findings. All patients met inclusion criteria and all enrolled in the study underwent the stage 2 procedure with implantation of the internal pulse generator. Median followup was 14.8 months (IQR 4.7–21.0).

Improvements

On Questionnaire after SNM. Figure 1 shows mean QOL scores for the entire patient cohort. The mean psychosocial QOL score and the total QOL score significantly improved after the initiation of SNM treatment, which persisted at the most recent followup. Physical QOL scores did not significantly improve after SNM treatment. Figure 2 shows BBD symptoms for the entire cohort. One patient failed to complete the preoperative BBD questionnaire and was not included in analyses of BBD symptoms. BBD symptoms significantly improved after the initiation of SNM treatment and again this effect persisted at the most recent followup. Subcohorts of patients who presented with specific symptoms of BBD (specific questions from the validated questionnaire) were analyzed with regard to improvement of these symptoms (supplementary figure, <http://jurology.com/>). Patients with daytime incontinence, urinary urgency, dysuria, nocturnal enuresis or fecal incontinence showed significant improvement with SNM treatment.

In BBD with Specific Urodynamic Findings. When comparing patients with vs without specific findings on preoperative urodynamic evaluation, those with who had uninhibited detrusor contractions preoperatively had significantly greater improvement in BBD scores than the rest of the cohort (fig. 3). The presence or absence of incomplete emptying or staccato voiding did not significantly impact BBD symptom improvement after SNM.

Medication Use

Ten patients (33%) were receiving anticholinergics or α -blockers immediately prior to SNM treatment. All 10 patients (100%) elected to discontinue these medications due to symptom improvement. Eight of 30 patients (26%) were on daily antibiotic prophylaxis immediately before SNM treatment. Six of these 8 patients (75%) elected to discontinue antibiotic prophylaxis due to symptom improvement.

Complications

Seven of 30 patients (23%) had a complication requiring operative intervention (see table). Patients 2, 10, 12 and 19 had 2 or more reoperative complications each. Only 1 of the 7 patients requested definitive removal of the device. All other patients elected replacement of necessary components for device function at reoperation due to satisfaction with treatment. One patient had ipsilateral calf pain and twitching, which was corrected by reprogramming the pulse generator. One patient became pregnant 2 months after implantation of the internal pulse generator. The device was deactivated for the duration of her pregnancy and reactivated after delivery. The most common complication was neurostimulator lead breakage, which was seen in 5 of 30 patients (17%). Lead breakage presented as return of preoperative symptoms. Subsequent interrogation of the device revealed elevated electrical impedance. Lead breakage occurred after minor trauma to the device in all cases. The group of patients with lead breakage had a significantly lower mean BMI than other patients (fig. 4). Maximum BMI in patients with lead breakage was 18.5 kg/m². Five of 14 patients (36%) with a BMI of 18.5 kg/m² or less had lead breakage.

DISCUSSION

In 2013 and 2015 the ICCS (International Children's Continence Society) recommended BBD as the preferred terminology for concomitant bowel and bladder disturbances, and discouraged use of the term dysfunctional elimination syndrome.¹⁰ BBD was defined as "a combination of functional bladder and bowel disturbances, including bladder overactivity (urge), increased or decreased voiding frequency, bladder underactivity or constipation."^{10,11} SNM was initially approved by the FDA to treat urinary urge incontinence in adults in 1997. Indications were expanded to include urinary

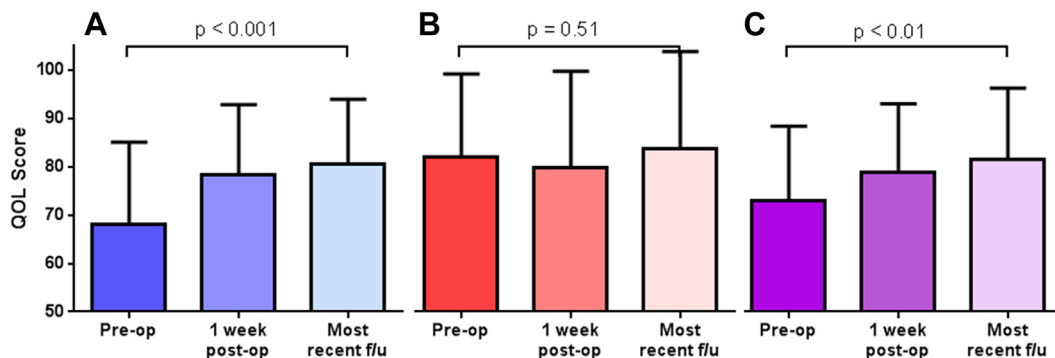


Figure 1. QOL scores before and after SNM. A, psychosocial. B, physical. C, total. *f/u*, followup.

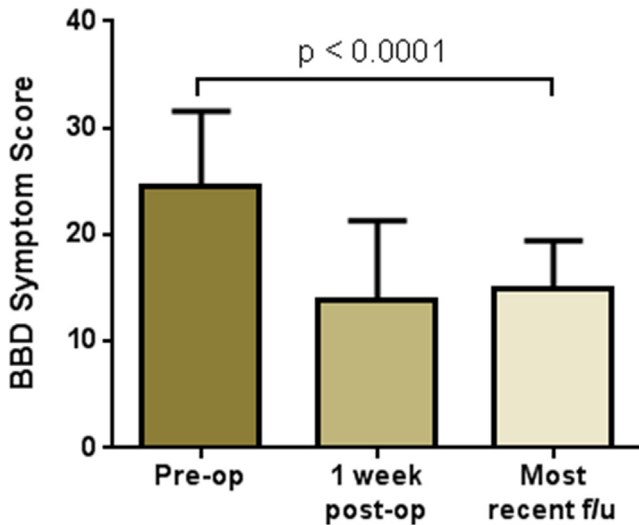


Figure 2. BBD symptom scores before and after SNM. f/u, followup.

urgency, frequency and nonobstructive urinary retention in 1999. In 2011 treatment of fecal incontinence with SNM was approved by the FDA as well. At this time the FDA states that the safety and efficacy of SNM have not been established for patients younger than 16 years and it is not approved for pediatric use. Numerous reports have been published regarding SNM in adults with randomized studies showing success rates of approximately 70% to 80% for the treatment of urinary symptoms. The mechanism of SNM is not clearly understood but it is thought to stabilize neurological mechanisms of voiding by stimulating afferent somatic sacral nerves.^{12,13}

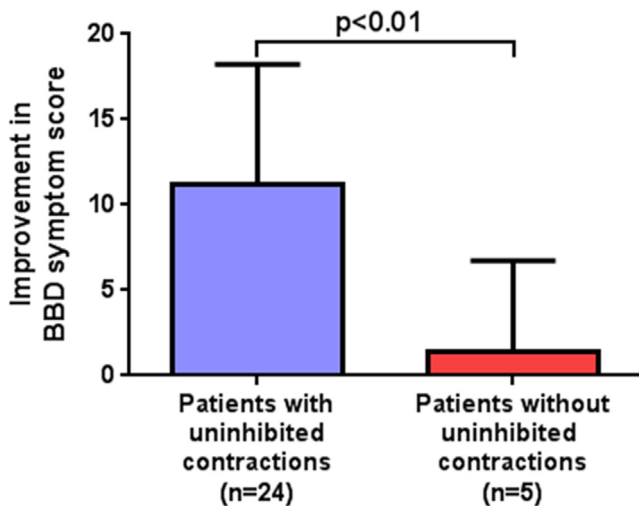


Figure 3. Improvement in BBD symptom score based on uninhibited detrusor contractions on preoperative urodynamic testing.

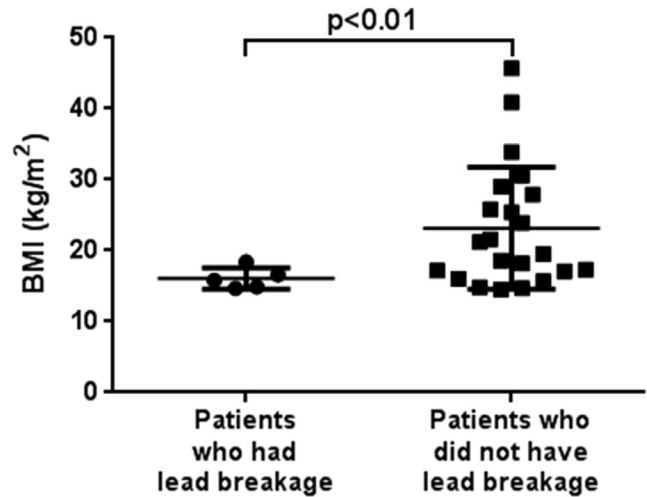


Figure 4. BMI of patients with vs without neurostimulator lead breakage events.

Yet several studies evaluating off label use of SNM in children have been published. Randomized studies of children with neurogenic lower urinary tract dysfunction have shown clinical improvement in those treated with SNM. These studies were unable to demonstrate objective improvement in urodynamic parameters compared to the control group or they showed improved cystometric capacity without improvement in other urodynamic parameters.^{1,2} For children with BBD without a neurogenic etiology several studies revealed overall efficacy of treatment as shown by patient reported improvement in symptoms. Urodynamic evaluation has not reportedly been used in a standardized manner in most studies.³⁻⁶ Studies of SNM treatment in children have had relatively high complication rates requiring operative intervention at 11% to 56%, most commonly due to device malfunction.¹⁻⁶

At our institution treatment of BBD begins with behavioral therapy, including timed voiding, double voiding, appropriate voiding posture and avoidance of dietary irritants. Aggressive treatment of constipation is initiated, given the well established relationship between constipation and urinary symptoms.¹⁴ At subsequent visits patients with refractory symptoms despite adequate treatment of constipation and adherence to behavioral therapy may be initiated on medications, including anticholinergics or α -blockers. Patients with evidence of pelvic floor dysfunction begin a pelvic floor biofeedback program. SNM at our institution is reserved for only the most refractory cases. This is illustrated in our series by the facts that only 30 patients underwent SNM of approximately 8,000 new visits for BBD (0.4%) during the study time frame and patients had a median of 7 clinic visits during 27 months prior to SNM. We stress the importance

Pt—Sex—Age No. (yrs)	Mos Since Implantation	Complication
1—F—6.5	Not applicable	Temporary lead dislodged when caught on door
2—M—8.7, 9.7	4, 16	Device erosion requiring generator removal, lead broken during fight with sibling
10—M—13.2, 14.0	25, 34	Lead broken while jumping on trampoline, lead broken while jumping on trampoline (again)
12—F—7.3, 8.3	19, 31	Lead broken during fight at playground, lead malfunction with no reported trauma
13—F—6.4	10	Lead broken after falling on device
14—M—8.5	18	Lead broken after falling on device
19—F—9.1, 9.2, 9.7	0, 1.5, 8	Foot paresthesia + twitching requiring lead repositioning, foot + leg pain from device migration requiring lead repositioning, recurrent leg pain + family requested permanent device removal claiming it never worked

of continued behavioral therapy after SNM. Patients at our institution continue the same medication regimen before and after SNM. They may elect to discontinue medications postoperatively after sufficient symptom improvement.

As we previously reported,⁶ patients with refractory BBD had significant improvement in BBD symptoms, and psychosocial and total QOL after SNM treatment as measured on validated questionnaires. This persisted at the longer followup in this study (median 14.8 months). Urodynamic evaluation preoperatively revealed that the group of patients with uninhibited detrusor contractions had significantly greater improvement in BBD symptoms than the rest of the cohort. We use this information to counsel families preoperatively but do not limit SNM treatment only to children with uninhibited detrusor contractions.

Our rate of reoperative complication of 23% is within the previously reported range of 11% to 56%.^{1–5} This rate may increase with time as seen in studies with longer followup.⁵ Most reoperations were due to device malfunction, which is consistent with the literature on children. We thought that children were more likely to cause device breakage due to minor trauma during normal childhood activity. A lower BMI correlated with a greater likelihood of device breakage. Theories for this finding include a greater activity level and decreased adiposity overlying the generator and leads. We use this information to counsel families of slimmer children but do not restrict physical activity or contraindicate SNM based on lower BMI.

Special considerations must be taken when performing SNM in children. The SNM device is currently incompatible with most MRI studies, only allowing for certain types of head MRI. The battery life of the SNM device is currently estimated at 3 to 9 years depending on the stimulation program used. In children this could necessitate multiple future operations to replace the generator unit when battery life expires. Children grow with time and it is currently not well established how this will impact device function or generator placement. In our series we have not yet seen any children who had the

pubertal growth spurt after implantation to evaluate this phenomenon. Female children have the potential for pregnancy as in 1 patient in our series. There is a case report of continuous use of SNM during pregnancy¹⁵ but data on the safety of this option are limited. We followed the manufacturer recommendations of device deactivation during pregnancy. Finally children require general anesthesia for device placement as they are unlikely to tolerate an office procedure or conscious sedation, which can be done in some adults for temporary lead placement. All of these factors should be discussed with the family of these patients preoperatively.

Our study certainly has limitations. Although this was a prospective study, we did not have a control group or randomize patients to treatment options. In future studies patients could be randomized between SNM and transcutaneous neuromodulation or placebo but families may be reluctant to enroll in a study where treatments vary so widely or placebo surgical intervention is possible. Patients underwent videourodynamic assessment preoperatively but to date none has undergone urodynamic evaluation postoperatively. Patients are reluctant to pursue further invasive testing when they think that treatment is working adequately. We have a relatively small cohort of patients due to our strict inclusion criteria and as such we have limited followup in the most recently implanted patients. There is also bias introduced when using questionnaires answered by the family as opposed to a standardized voiding diary with less subjective measures.

CONCLUSIONS

SNM significantly improves QOL and severity of symptoms in children with BBD refractory to conventional treatments. Although it is not currently a FDA approved treatment, SNM is an option for this population. Patients are more likely to gain substantial benefit from SNM if they show uninhibited bladder contractions on preoperative urodynamic evaluation. Children have a fairly high rate of lead breakage requiring operative revision, which was seen after minor trauma in those with a lower BMI.

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EDITORIAL COMMENT

This study, as others, demonstrates the efficacy of SNM for the treatment of refractory BBD in the pediatric population. The problem with lead breakage merits discussion. I believe that this risk can be decreased by implanting the implantable pulse generator in the buttocks ipsilateral to the lead insertion site. Leads that cross the sacrum/lumbar spine are potentially at more risk for fracture in this region.

Parents often inquire whether they should restrict the activities of the child after the device is implanted. Many of these children have self-limited their activities before insertion due to

fear of incontinence and bathroom inaccessibility. Once liberated from these concerns many rapidly and joyfully reenter social and sporting activities. To force them to limit these activities to protect the sacral lead in my opinion diminishes QOL and defeats one of the primary goals of the procedure.

David R. Vandersteen

*Pediatric Surgical Associates, Ltd.
Minneapolis, Minnesota
Pediatric Urology
Mayo Graduate School of Medicine
Rochester, Minnesota*