

Research Article

Reduction of Nocturia after Sacral Neuromodulation Therapy for Overactive Bladder

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Abstract

Objective: To examine whether improvements in nocturia are seen following sacral neuromodulation therapy in patients treated for other lower urinary tract symptoms such as urinary urgency/frequency or urge urinary incontinence.

Methods: Eighty two patients (72 women, 10 men) underwent successful sacral nerve test stimulation followed by permanent implantable pulse generator (IPG) implantation from March 2000 to October 2009. The number of nocturia episodes was recorded between pre- and postoperative periods and were stratified by age and severity of preoperative nocturia. Use of anticholinergic medication was recorded.

Results: When stratified by age (<50, 50-69, ≥70), all groups experienced a significant decrease in nocturia episodes per night (1.82, 2.39, 1.63, respectively, $p < 0.01$). Age ≥70 predicted poorer response to neuromodulation with respect to nocturia ($p < 0.01$). Patients presenting with minimal nocturia were less likely to experience ≥50% decrease in nocturia episodes. Success rates were 44.4%, 66.7%, and 69.2% for groups with <3 voids, 3-5 voids, and >5 voids per night, respectively ($p < 0.05$, $p = 0.191$, and $p = 0.448$).

Conclusions: Reductions in nocturia were noted in each group studied. Patients aged ≥70 and those with <3 preoperative nocturia episodes were not as likely to see benefit after neuromodulation. Although no causal relationship can be proven due to the limitations of the study, it appears nocturia improves following sacral neuromodulation.

INTRODUCTION

The treatment of nocturia is defined as waking at night to void [1]. Nocturia is important due to its detrimental effects on general health, and on overall quality of life. Increases in the number of voids per night have been associated with negative effects on sleep and health related quality of life [2]. An Austrian study found that 66.9% of women and 62.2% of men with nocturia reported a negative impact from this symptom on their quality of life [3]. Lower Urinary Tract Symptoms (LUTS) have also been shown to be associated with psychiatric morbidity, with nocturia as a significant predictor for anxiety [4]. A large survey of the U.S. population also demonstrated that the prevalence of nocturia increases with age, and that nocturia affects men and women equally [2]. Increasing severity of nocturia can also result in a greater risk for falls [5]. Nocturia, more than two times per night has been associated with an increased risk for hip fractures in men [6]. Nocturia has even been associated with an increased

mortality rate in the elderly who void three or more times per night [7].

Nocturia is often a difficult problem to treat and therefore it continues to be bothersome for many patients despite therapy. Sacral neuromodulation has been shown to improve other lower urinary tract symptoms such as urinary urgency incontinence and urinary urgency/frequency [8]. Sacral neuromodulation has been proven effective for idiopathic urgency-frequency [9] and has been shown to be effective in treating dysfunctional voiding (frequency and nocturia) [10].

Although nocturia is a symptom associated with many of these indications for sacral neuromodulation, little has been documented regarding the effect of neuromodulation on nocturia, or how the severity of nocturia might predict response to sacral neuromodulation. In other words, does improvement in urinary urgency and frequency or urge urinary incontinence

after sacral neuromodulation imply that nocturia will improve as well? We hypothesized that nocturia will improve following sacral neuromodulation and this potentially offers a new tool in the multi-modal therapy of nocturia. If effective, patients could be counseled that in addition to possible benefit for urinary urgency, frequency, urgency incontinence, and non-obstructive urinary retention, neuromodulation may offer some improvement in nocturia symptoms as well. We also hypothesized that patients will have less improvement in nocturia with increased age at time of device implantation.

MATERIALS AND METHODS

Upon Institutional Review Board approval, we performed a retrospective analysis of 211 patients at the University of Iowa Hospitals and Clinics who underwent permanent InterStim® (Medtronic, Minneapolis, MN) device implantation between March 2000 and October 2009. All patients had previously and previously failed behavioral modification therapy, pelvic floor exercises, and pharmacologic therapy. This included counseling all patients to reduce bladder irritants, including caffeine, and reducing nocturnal water intake 4 hours prior to going to bed. Indications for sacral neuromodulation were not mutually exclusive and patients often had more than one indication at time of presentation. All patients underwent baseline assessment including complete medical history, physical examination, urodynamic studies, and a 3-day preoperative voiding diary to characterize voiding behavior and symptoms. All patients underwent a period of successful test stimulation. Nocturia was assessed by the question "how many times do you get up at night to urinate?" This was thought to be more representative of nocturia than the bladder diary due to variability in patient sleep/wake cycles. This was asked at the preoperative visit and at the most recent follow up visit, which differed for some patients. Any answer of one time or greater was considered "nocturia" according to ICS terminology [1]. Data was extracted from electronic medical records and urodynamic study reports. Patients with a diagnosis of preoperative urinary retention (n=42) and neurogenic bladder (n=16) were excluded from study, as were 71 patients who failed stage 1 test stimulation or had incomplete data. Eighty-two patients were included for analysis. Data was compiled and organized in a database using Microsoft Access and Microsoft Excel (Microsoft Corp., Redmond, WA).

Patients considered for permanent IPG implantation were required to demonstrate at least 50% improvement in urinary symptoms during a 7- to 21-day test period. Two methods of testing were used. Prior to September 2002, a percutaneous test lead was unilaterally placed in the S3 or S4 sacral foramen.

This procedure was replaced in 2003 with a staged procedure, in which the permanent 4-contact lead was implanted during stage I under anesthesia, followed by a 1- to 3-week test period with an external pulse generator.

As nocturia is often considered multifactorial in etiology, an attempt was made to characterize patients with pre-existing risk factors for nocturia, such as age and anticholinergic use. It should be noted that nocturia was not taken into account when the decision to implant a permanent IPG was made. Improvement in nocturia was reported as the preoperative number of nocturia episodes compared with the most recent postoperative number of nocturia episodes. Improvement in nocturia was analyzed by 2-tail t-test. Devices removed but later replaced with persistent benefit were also considered successful. When stratified by preoperative episodes of nocturia, a successful outcome was defined by a decrease of 50% or more in nocturia episodes postoperatively.

RESULTS

Data from 10 men (12.2%) and 72 women (81.8%) were reviewed. Mean patient age was 59.4 (± 14.4) years. Mean age for men was 61.6 (± 15.1) years and mean age for women was 59.1 (± 14.4) years. 44/82 (54%) of patients were taking some form of anticholinergic medication prior to implantation, while this only decreased to 39/82 (48%) following successful implantation. Patients were not encouraged to stop these medications post operatively. The mean follow up time was 36.4 (± 35.6) months. When stratified by age (<50, 50-69, ≥ 70), all groups experienced a significant decrease in nocturia episodes per night ($p < 0.01$; Table 1). Patients age <50 (20 patients) experienced a drop from an average of 3.25 preoperative voids per night to an average of 1.43 voids per night (difference of 1.82 [± 0.77 95% CI] voids per night, $p < 0.01$). Patients between the ages of 50-69 years had an average of 4.56 voids per night preoperatively, and an average of 2.17 voids per night postoperatively (difference of 2.39 [± 1.03] voids per night, $p < 0.01$). Patients age ≥ 70 years had a preoperative average of 3.65 voids per night, and an average of 2.02 voids per night postoperatively (difference of 1.63 [± 0.66], $p < 0.01$. Age ≥ 70 predicted poorer response to neuromodulation with respect to nocturia, where 62% experienced a >50% reduction in nocturia compared with 90% and 86% for the other 2 groups ($p < 0.01$).

Finally, severity of preoperative nocturia was examined as a predictor for post operative improvement with sacral neuromodulation by stratifying patients according to the number of preoperative voids per night as a measure of nocturia severity (Table 2). Sacral neuromodulation demonstrated success rates of 44.4%, 66.7%, and 69.2% for groups with <3 voids, 3-5 voids, and >5 voids per night, respectively. Success was defined as a

Table 1: Effect of age on nocturia in patients treated with sacral neuromodulation.

Age Group	Preoperative Nocturia Episodes	Post-Operative Nocturia Episodes	Post-Operative average improvement in Nocturia	Number of patients experiencing 50% reduction in Nocturia Post Operatively
< 50 years	3.25 \pm 0.64	1.42 \pm 0.54 $p=0.00005$	1.82 \pm 0.77	18/20 = 90% $p=0.1733$
50-69 years	4.56 \pm 1.12	2.17 \pm 0.61 $p=0.00036$	2.39 \pm 1.03	31/36 = 86% $p=0.1763$
≥ 70 years	3.65 \pm 0.69	2.01 \pm 0.66 $p=0.00093$	1.63 \pm 0.66	16/26 = 62% $p=0.0070$

\pm denotes 95% confidence interval.

Table 2: Effect of preoperative severity of nocturia in patients treated with sacral neuromodulation.

Severity (episodes per night)	Number of patients experiencing $\geq 50\%$ reduction in nocturia postoperatively
<3	12/27 (44.4%)
3-5	28/42 (66.7%)
>5	9/13 (69.2%)

For each group, Student's t test was used to compare combined results from the other 2 groups. The two more severely affected groups had significant benefit compared to severity <3 group ($p=0.046$).

50% or more reduction in nocturia episodes. Patients with mild nocturia preoperatively could expect relatively less improvement postoperatively compared with the more severely affected groups ($p<0.05$). The average improvement across groups was 0.59 ± 0.37 (95% CI), 2.02 ± 0.48 (95% CI), and 4.92 ± 1.69 (95% CI) voids per night, respectively.

DISCUSSION

As hypothesized, all of the subgroups analyzed experienced significant reductions in the severity of nocturia secondary to placement of the sacral neuromodulation device. It should be noted that this is a highly selected set of patients who have already experienced an initial favorable response to sacral neuromodulation for either urgency/frequency or urgency incontinence.

Not all patients had stopped anticholinergic medication, despite successful sacral neuromodulation, suggesting a role for multimodal therapy. This also confounds the effect of sacral neuromodulation on nocturia, as anticholinergics clearly will affect nocturia. When patients were stratified by age, all groups experienced statistically significant reductions in nocturia. Given data suggesting that nocturia is worse in the elderly and that sacral neuromodulation tends to have reduced efficacy in older individuals [11], we hypothesized that the older groups of patients would have less improvement than younger patients. Indeed, the data reflects a trend in this direction with the oldest group of patients (>70 years) experiencing the lowest degree of improvement in nocturia after device implantation ($p=0.0070$). Others have found different factors have affected success rates with sacral neuromodulation, such as age >55 and more than three chronic medical conditions [11].

Another hypothesis explored in this study was that patients with more severe nocturia would experience poorer response to sacral neuromodulation. Just the opposite was demonstrated, with patients suffering the worst nocturia (>5 voids per night) having the highest success rates (69.2%) compared with those having the least nocturia (<3 episodes per night) having the lowest (44.4%, $p=0.046$). We believe that this is partially due to how "success" is defined. For purposes of the study, a 50% or greater reduction in nocturia episodes was considered success. The least affected group, then, had to improve to 0-1 voids per night and this may be more difficult to achieve than 2-3 voids per night. Nonetheless, this suggests that there is a point of diminishing returns when treating nocturia with sacral neuromodulation and that mild nocturia may not respond as well as severe nocturia. Further review of the data revealed 4 patients who reported

0 nocturia episodes post op ("cured") who reported a mean of 3.13 pre op nocturia episodes. It is possible that nocturia is multi-factorial in etiology and perhaps some etiologies respond well (overactive bladder) while others, such as lower extremity edema returning to the vascular space, do not respond as well.

Several limitations to this study deserve mention. This was a retrospective chart review that relied on several years of records, generated by different physicians. Many patients were excluded for incomplete data and only those with successful stage 1 test stimulation were included for postoperative analysis, which introduces bias into the results. It is likely that success rates are much higher in this investigation than they might be for patients considered for analysis prior to stage 1 test stimulation. No consideration was made for those suffering from nocturnal polyuria, which might affect their response to neuromodulation, but regardless the patients in this series responded well. All patients were counseled on fluid restriction, but no measures were taken to enforce or verify compliance. This might best represent real-world clinical practice, possibly making the results more relevant for general clinical practice. Data on diuretic use as well as obstructive sleep apnea was also not available and these patients might be expected to pose a higher risk of nocturia.

CONCLUSIONS

Reductions in nocturia were noted in each group studied. Patients aged ≥ 70 and those with <3 preoperative nocturia episodes were not as likely to see benefit after neuromodulation. Although no causal relationship can be proven due to the limitations of the study, it appears nocturia improves following sacral neuromodulation. Sacral neuromodulation might become a useful adjunct therapy for patients with severe nocturia, but randomized, placebo controlled data is needed with better etiologic classification of the nocturia is needed to make a robust conclusion. As the population ages and older adults are living more active lifestyles, we anticipate more demand for nocturia treatment. Further data derived from a prospective study could provide more robust findings in this area.

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