Sacral neuromodulation outcomes for the treatment of refractory idiopathic detrusor overactivity stratified by indication: Lack of anticholinergic efficacy versus intolerability

Tanya Davis, MD; Iryna Makovey; Michael L. Guralnick MD, FRCSC; R. Corey O'Connor, MD

Department of Urology, Medical College of Wisconsin, Milwaukee, Wisconsin

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Abstract

Introduction: Patients may fail oral overactive bladder therapies due to either poor drug efficacy or intolerability. We determined if the success of sacral neuromodulation varies if performed secondary to lack of anticholinergic efficacy versus drug intolerability.

Methods: A retrospective review was performed on 152 patients undergoing staged sacral neuromodulation from 2004 to 2010 for refractory idiopathic detrusor overactivity with or without urge incontinence. Outcomes following sacral neuromodulation trials were compared based on the primary indication for anticholinergic failure: lack of drug efficacy versus intolerable side effects.

Results: Overall, successful sacral neuromodulation trials were reported in 70% (106/152) of patients. Successful outcomes were noted in 70% (89/128) and 71% (17/24) of patients with poor anticholinergic efficacy and drug intolerability, respectively ($p = \text{NS}$).

Conclusions: We found no significant difference in outcome success in patients undergoing sacral neuromodulation trials for refractory detrusor overactivity due to lack of anticholinergic efficacy versus intolerability.

Introduction

Initial management of overactive bladder (OAB) often involves behavioural modification and anticholinergic medications. Anticholinergic medications competitively inhibit muscarinic receptors in the detrusor and urothelium to suppress overactive detrusor contractions and decrease sensation.¹

Pharmacotherapy, however, is not successful for all patients due to either poor drug efficacy or intolerable side effects, such as dry mouth and constipation, secondary to muscarinic blockade elsewhere in the body.^{2,3} When initial conservative therapy fails, surgical therapies such as sacral neuromodulation (SNM) or intradetrusor injections of botulinum toxin A (BTX-A) may be employed. One of the main

mechanisms of action of intradetrusor BTX-A is the prevention of presynaptic acetylcholine neurotransmitter release at the neuromuscular junction. Thus, like anticholinergic medications, intradetrusor BTX-A involves the blockade of acetylcholine neurotransmission in the bladder. We previously found that more patients responded to intradetrusor BTX-A if their indication for the procedure was anticholinergic intolerability as opposed to lack of anticholinergic efficacy, and hypothesized that the similar mechanisms of action may have partly explained this finding.⁴ SNM, a proven second-line treatment for OAB symptoms in patients refractory to anticholinergic drugs,⁵ is postulated to act by suppressing or enhancing the sacral afferent and efferent bladder nerves to modulate storage and voiding reflexes.⁶ It has a different mechanism of action compared to anticholinergic medications and intradetrusor BTX-A. The purpose of this study is to evaluate our outcomes with SNM for refractory OAB stratified by indication: lack of anticholinergic efficacy versus drug intolerability. Because of the differing mechanisms of action, we hypothesize that the difference in response rates that we previously noted with intradetrusor BTX-A will not be noted with SNM.

Methods

After institutional review board approval, a retrospective chart review was performed for all patients undergoing staged SNM (InterStim, Medtronic Inc., Minneapolis, MN) at a single tertiary care centre from 2003 to 2010 for the management of idiopathic OAB symptoms refractory to behavioural modification and anticholinergic medications. All patients were evaluated with complete history and physical examination, urinalysis, post-void bladder ultrasound and video urodynamic studies. Inclusion criteria included video urodynamic studies proven detrusor overactivity, negative urinalysis and failure of at least two or more separate four-week trials of oral anticholinergic medications at maximally approved dosages. Exclusion criteria were age <18 years,

incomplete bladder emptying measuring >100 mL, bladder outlet obstruction, impaired bladder compliance, primary neurologic disease, previous pelvic radiotherapy or history of bladder outlet surgery.

Staged SNM was performed in the previously reported fashion,⁷ with unilateral or bilateral tined S3 lead placement. A two-week trial period of unilateral lead stimulation was used to assess efficacy. Trial stimulation was deemed successful if a >50% improvement in OAB symptoms was noted based on objective and subjective measures, including 24-hour bladder diary, 24-hour pad weights and patient-reported symptom improvement.

Patients were divided into two cohorts based on the patient-reported primary reason for anticholinergic failure: lack of medication efficacy or intolerability due to drug side effects. The outcomes were statistically analyzed using either Student's *t* or Fisher's exact test.

Results

A total of 152 patients were included in the study. We tallied demographic data, American Society of Anesthesiologists (ASA) classification results and anticholinergic medication usage for the two groups (Table 1). Overall, successful SNM implantation trials were reported in 70% (106/152) of patients. When divided into cohorts based on reason for medication failure, success rates were 70% (89/128) and 71% (17/24) for patients with poor anticholinergic efficacy and drug intolerability, respectively ($p = \text{NS}$).

Complications were reported by 12/152 (8%) patients, including prolonged pain at the SNM battery/incision site ($n = 6$) and wound infection ($n = 6$). Prolonged pain over the SNM battery following stage II SNM was initially managed with oral and topical pain medications. Patients that failed conservative treatment underwent surgical repositioning of the SNM battery. SNM infection (four patients following stage I SNM and two patients after stage II SNM) required complete device explantation with delayed reimplantation for all patients.

Discussion

First-line anticholinergic therapy for the management of overactive bladder may be ineffective for some patients due to poor efficacy or intolerable side effects. Other treatments,

including BTX-A injection and SNS, have been shown to be effective, second-line agents for patients with symptoms refractory to medications.⁸ Currently, no published study has explored whether or not the reason for anticholinergic failure can be used to help predict the rate of SNM success. We reviewed the results of stage I SNM implantation for the management of idiopathic detrusor overactivity refractory to anticholinergic medications due to poor drug efficacy versus lack of tolerability. Our findings showed no significant difference in outcomes when comparing patients undergoing SNS trials due to lack of anticholinergic efficacy versus drug intolerability (70% vs. 71%, $p = \text{NS}$).

We previously demonstrated that intradetrusor BTX-A injections are more successful for the treatment of refractory OAB if performed in patients with anticholinergic intolerability rather than poor drug efficacy.⁴ BTX-A and anticholinergic drugs both decrease detrusor contractions by preventing acetylcholine from reaching the muscarinic receptors. As a result of similar mechanisms of action, we suspected that patients who responded to anticholinergic medications may be more likely to respond to BTX-A. The current study did not support the same findings. We postulated that the results may be due to the differing mechanisms of action of anticholinergic medications and SNM. Anticholinergic drugs primarily prevent detrusor contraction and decrease bladder sensation by blocking muscarinic receptors in the detrusor and urothelium.¹ SNM is believed to target the afferent and efferent bladder nerves, modulate the balance between bladder inhibition and excitation and, therefore, reduce OAB symptoms.^{6,9} As a result of the differing mechanisms, the success of SNM should not be predicted based on anticholinergic failure.

Success rates of SNM for the management of refractory OAB symptoms range from 53% to 80%.¹⁰⁻¹² Our success rates in this study fall within the published norms. Several authors have demonstrated that advanced patient age, male gender, increased duration of symptoms and the presence of concomitant medical comorbidities decrease the likelihood of success following SNM.¹³⁻¹⁶ The two cohorts examined in our study were similar in age, gender distribution and overall health. As a result, we do not believe that sampling error contributed to our results. The small sample size and retrospective design, however, do limit the strength of the findings. Additionally, our described success rates reflect findings from stage I SNM trials, not permanently implanted

Table 1. Patient demographics and anticholinergic medication use

	Total (n=152)	Lack of efficacy (n=128)	Intolerable side effects (n=24)	<i>p</i> value
Age in years (range)	55.1 (18-86)	54.9 (18-86)	55.8 (24-83)	NS
Gender (F:M)	125:27	105:23	20:4	NS
Average medications attempted (range)	3.0 (2-6)	3.0 (2-6)	3.1 (2-6)	NS
ASA classification (range)	2.2 (1-4)	2.2 (1-4)	2.1 (1-4)	NS

F: female; M: male; ASA: American Society of Anesthesiologists; NS: not significant.

devices. Our conclusions cannot be extended to long-term results. As such, this is more of a hypothesis-generating study than a conclusive one. Additional prospective studies are warranted.

Conclusions

No significant difference in outcomes was observed in patients undergoing SNM trials for the management of OAB due to lack of anticholinergic efficacy versus drug intolerability. The findings may be secondary to different mechanisms of actions between anticholinergics and SNM. Prospective, multicentre trials are needed to strengthen the results.

Competing interests: None declared.

This paper has been peer-reviewed.

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Correspondence: Dr. Michael L. Guralnick, Associate Professor of Urology, Medical College of Wisconsin, 9200 W. Wisconsin Ave, Milwaukee, WI 53226; fax: 414-805-0771; mguralni@mcw.edu