

Sacral neuromodulation for refractory overactive bladder after prior intravesical onabotulinumtoxinA treatment

Nathan Hoag^{1*} | Sophie Plagakis² | Samantha Pillay³ | Ailsa Wilson Edwards³ |
Johan Gani¹

¹ Austin Hospital, Melbourne, Australia

² Repatriation General Hospital, Adelaide, Australia

³ Continence Matters, Adelaide, Australia

*Correspondence

Nathan Hoag, MD, FRCSC, Austin Hospital, 145 Studley Rd, Heidelberg, Victoria 3084, Australia
Email: nathanhoag2@gmail.com

AIMS: Sacral neuromodulation (SNM) is a well-established treatment modality for refractory overactive bladder (OAB). There is a paucity of evidence examining the use of SNM in patients who have received prior intravesical onabotulinumtoxinA (BTXA) treatment. We aim to review those patients who underwent SNM for refractory OAB following treatment with BTXA.

METHODS: A retrospective review was conducted to identify patients who had undergone prior intradetrusor BTXA for refractory OAB, then subsequent first-stage SNM. Patient demographics, number/dosage of BTXA, voiding diaries, and patient global impression of improvement (PGI-I) scores were recorded. Successful first-stage SNM was defined as subjective patient improvement of greater than 50%. Patient satisfaction and device use at last follow-up was noted.

RESULTS: Eighty-three patients were identified having undergone SNM for OAB, of which 36 had prior BTXA treatment and were included in the series. 23/36 (63.9%) of patients had successful first-stage SNM, and underwent insertion of implantable pulse generator, compared to 33/47 (70.2%) in those who had never been treated with BTXA ($P = 0.5$). Mean PGI-I score was 2.6 (range 1–4). With a mean follow up of 29.1 months (range 12–53), 17/23 (73.9%) were satisfied, and using the device at last follow-up.

CONCLUSION: SNM is a suitable treatment option in those patients who have had prior BTXA treatment for refractory OAB, even in those for whom BTXA proved ineffective. Success rates were within the published range, and comparable to our own results, for SNM in OAB patients without prior BTXA treatment.

KEYWORDS

botulinum toxin A, overactive bladder, sacral neuromodulation, urgency urinary incontinence

1 | INTRODUCTION

Overactive bladder (OAB) is a common condition characterized by urinary frequency, urgency, and urge incontinence,

and contributes a significant impact on healthcare systems.¹ Its prevalence was noted to be approximately 16.5% in two large studies of American and European adults.^{1,2}

Initial treatment options for OAB include first-line behavioral therapy, and second-line oral medications (antimuscarinics and beta-3-agonists). Third-line options include intradetrusor onabotulinumtoxinA (BTXA), sacral neuromodulation (SNM), and percutaneous tibial nerve stimulation (PTNS).³

BTXA injections have demonstrated efficacy in the treatment of refractory OAB, and have become well

Dr. John Heesakkers led the peer-review process as the Associate Editor responsible for the paper.

This work was performed at Austin Health (Melbourne) and Continence Matters (Adelaide).

This paper has obtained Institutional Ethics Review Board approval.

established in its treatment algorithm.⁴ There is, however, a significant proportion of patients who discontinue treatment, mainly due to lack of efficacy or issues with urinary retention.⁵

The safety and efficacy of SNM for refractory OAB has been well-documented in the literature.⁶ Success rates, have been reported between 64% and 88%.⁷ To date, there has been little data on the efficacy of SNM specifically in those patients who have discontinued BTXA treatment. In a series of 20 patients, Smits et al showed a 70% success rate for first-stage SNM in patients previously treated with BTXA.⁸ In addition, of the 14 patients who went on to subsequent insertion of permanent implantable pulse generator (IPG) in their series, 11 (79%) were noted to be satisfied at 1 year follow-up.⁸

We aim to review the efficacy of SNM in patients with refractory overactive bladder who have received prior BTXA treatment.

2 | MATERIALS AND METHODS

After institutional ethics approval, a retrospective review of prospectively collected data was performed between three surgeons in Adelaide and Melbourne, Australia during the years 2010–2015. Following favorable evaluation for suitability of SNM as a treatment modality for urodynamic-proven, refractory, idiopathic OAB, patients underwent first-stage tined lead placement of a unilateral S3 electrode under general anesthetic. Second stage, when performed after successful 2-week trial, comprised of insertion of IPG under either local or general anesthesia.

Patient demographics were recorded for consecutive patients who underwent SNM for refractory idiopathic OAB. History of prior BTXA treatment was noted. Details regarding SNM were documented, to include time from last botox until first-stage SNM, percentage improvement in subjective symptoms, IPG insertion, follow-up duration, as well as voiding diaries before and during the first-stage testing

period, and modified patient global impression of improvement (PGI-I)⁹ scores were recorded at 3 month follow-up visit.

Information was tabulated, and descriptive statistics were utilized to determine success rates of SNM in those patients who received prior BTXA treatment (as defined by subjective symptom or incontinence episode improvement greater than 50%). This was compared to our baseline success rates (33/47, 70.2%) in patients with refractory OAB without prior BTXA treatment. Statistical analysis was carried out using the χ^2 , and Fisher's exact tests to compare the groups, with significance set at $P < 0.05$.

3 | RESULTS

Eighty-three consecutive patients were identified having undergone SNM for refractory idiopathic OAB, with 36/83 (43.4%) having had prior BTXA treatment. Patient numbers, demographic information, outcomes, and information about BTXA treatments are summarized in Table 1, while complete individual patient data are shown in Table 2.

In this series, 25/36 (69.4%) had discontinued BTXA due to ineffectiveness, 9/36 (25.0%) due to retention (or elevated post-void residual volumes), and 2/36 (5.6%) due to possible adverse reaction. The success rate for first-stage SNM in BTXA naïve patients was 33/47 (70.2%). In patients who had failed BTXA treatment prior to SNM, the success rate of first-stage SNM was 23/36 (63.9%) ($P = 0.5$). In the subset of patients for whom BTXA had proven “ineffective,” 16/25 (64.0%) ($P = 0.6$) had a successful first-stage test. In those patients who had undergone prior BTXA treatment, success rate of first-stage SNM was 13/19 (68.4%) in those who had two or fewer BTXA treatments, compared to 10/17 (58.8%) in those had three or more treatments ($P = 0.5$). No statistically significant differences in age, gender, or OAB “wet versus dry,” noted between the groups with, and without prior BTXA treatment.

TABLE 1 Summary of patient cohort demographics and treatment information, with, and without prior BTXA treatment

	“Prior BTXA”	“BTXA-naïve”	<i>P</i> -value
Consecutive patients undergoing SNM	36/83 (43.4%)	47/83 (56.6%)	—
Gender	35/36 Female (97.2%)	42/47 Female (89.4%)	$P = 0.23$
Mean age	60.9 years (range 22–86)	56.9 (range 18–84)	$P = 0.26$
“OAB-wet”	34/36 (94.4%)	45/47 (95.7%)	$P > 0.9$
Successful stage 1 SNM trial	23/36 (63.9%)	33/47 (70.2%)	$P = 0.5$
Average PGI-I score (range)	2.6 (1–4)	2.3 (1–4)	$P = 0.2$
Satisfied and using device at last follow-up	17/23 (73.9%)	25/33 (75.8%)	$P = 0.9$
Mean duration of last BTXA to SNM	11.8 months (range 3–30)	n/a	—
Mean prior botox treatments	2.83 (range 1–13)	n/a	—
Patients with ≤ 2 BTXA treatments	19/36 (52.8%)	n/a	—

BTXA, onabotulinumtoxinA; SNM, sacral neuromodulation; PGI-I, patient global impression of improvement; OAB, overactive bladder.

TABLE 2 Individual patient data for those undergoing sacral neuromodulation following prior intravesical onabotulinumtoxinA treatment

Patient #	Age/Sex	# of BTXA treatments (dose (units))	Time from last BTXA to SNM (months)	Reason for stopping BTXA	Improvement (%)	Insertion of IPG? Yes/No	PGI-I score	Follow-up (months)	Continued use at last follow-up?
1	62/F	1 (100)	9	Retention	>50	Yes	2	33	Yes
2	58/F	3 (100)	9	Retention	>50	Yes	3	18	Yes
3	71/F	3 (100–200)	14	Ineffective	<50	No	n/a	n/a	n/a
4	53/F	1 (100)	7	Ineffective	>75	Yes	2	28	Yes
5	77/F	4 (100–300)	8	Ineffective	>50	Yes	4	21	No
6	86/F	1 (100)	24	Ineffective	>50	Yes	3	15	Yes
7	78/F	1 (200)	3	Adverse reaction	>50	Yes	3	35	Yes
8	57/F	4 (100–200)	26	Retention	>75	Yes	1	26	Yes
9	65/F	1 (100)	16	Ineffective	>50	Yes	2	14	Yes
10	67/F	2 (100)	12	Retention	<50	No	n/a	n/a	n/a
11	58/F	4 (200–300)	15	Ineffective	<50	No	n/a	n/a	n/a
12	76/F	2 (100)	30	Retention	<50	No	n/a	n/a	n/a
13	61/F	1 (200)	15	Retention	<50	No	n/a	n/a	n/a
14	50/F	13 (300)	5	Ineffective	>75	Yes	1	37	Yes
15	27/F	5 (50–200)	10	Ineffective	>50	Yes	1	39	Yes
16	82/F	8 (200)	7	Ineffective	<50	No	n/a	n/a	n/a
17	74/F	5 (100)	11	Ineffective	<50	No	n/a	n/a	n/a
18	82/F	3 (100–300)	12	Ineffective	<50	No	n/a	n/a	n/a
19	66/F	2 (100)	5	Ineffective	>50	Yes	1	49	Yes
20	61/F	3 (100)	9	Ineffective	>75	Yes	1	36	Yes
21	62/F	4 (100)	4	Retention	>50	Yes	4	53	No
22	84/F	1 (100)	8	Ineffective	<50	No	n/a	n/a	n/a
23	53/F	3 (100)	3	Ineffective	>75	Yes	n/a	26	No
24	44/F	4 (100)	12	Ineffective	<50	No	n/a	n/a	n/a
25	74/F	2 (100)	14	Ineffective	>50	Yes	4	12	No
26	40/F	3 (300)	24	Ineffective	<50	No	n/a	n/a	n/a
27	41/F	1 (100)	10	Ineffective	>50	Yes	3	20	Yes
28	41/F	4 (100)	3	Ineffective	>50	Yes	n/a	24	Yes
29	86/F	2 (100)	13	Ineffective	>50	Yes	3	37	Yes
30	22/F	2 (100–300)	5	Ineffective	<50	No	n/a	n/a	n/a
31	55/F	1 (100)	10	Retention	>75	Yes	4	41	No
32	45/M	1 (100)	13	Retention	<50	No	n/a	n/a	No
33	44/F	1 (100)	9	Ineffective	>50	Yes	3	33	Yes
34	53/F	3 (100)	24	Ineffective	>75	Yes	4	14	No
35	73/F	2 (100)	12	Ineffective	100	Yes	4	45	Yes
36	66/F	1 (100)	12	Adverse reaction	>75	Yes	1	14	Yes

BTXA, onabotulinumtoxinA; SNM, sacral neuromodulation; PGI-I, patient global impression of improvement.

Of 23 patients who had a successful first-stage S3 tined lead placement trial and subsequent IPG placement, 17 (73.9%) were satisfied and using the device at last follow-up (mean 29.1 months, range 12–53). Three patients (13%) have required revision procedures, to date. Average PGI-I score at three months was 2.6 (range 1–4).

4 | DISCUSSION

The American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) guidelines updated in 2015, list both BTXA and SNM as third-line treatment options for refractory idiopathic OAB.³

It is known that a significant proportion of patients with OAB prescribed oral medications will cease therapy. A Canadian study noted over 12 months, the persistence rate of mirabegron was 39%, compared to 14–35% for antimuscarinics.¹⁰ While mirabegron is reportedly better tolerated than oral anticholinergics, a separate study showed that discontinuation rates remain high due to insufficient efficacy, with only 48% remaining on treatment at 6 months.¹¹ Additionally, discontinuation of BTXA treatment is not infrequent, with up to 37% stopping the treatment after two injections.⁵

One might assume that in those patients who have failed conservative management, oral medications, and intradetrusor BTXA, may have an inherently recalcitrant bladder. The results demonstrate, however, that SNM remains a reasonable treatment option in those who have failed BTXA for refractory OAB. While reasons for this remain unknown, it may be explained by the fact that BTXA and SNM exert their effects by different mechanisms of action. While BTXA acts locally, SNM retains a more central effect, making those who have failed BTXA still suitable for a trial of SNM.

Our success rate of 23/36 (63.9%) and 16/25 (64.0%) for prior BTXA and prior “ineffective” BTXA, respectively, did not differ significantly from our own success rates of 33/47 (70.2%) in BTXA-naïve patients. In addition, our success rates in all groups of patients were in keeping with published success ranges in the literature.^{12–14}

The PGI-I score, recorded at three months after insertion of IPG, demonstrated a mean of 2.6 (between “a little better” and “much better”). With a range of 1–4, it is obvious that the subjective nature of improvement is variable between patients, and counseling on expectations should be carried out accordingly. As 17/23 (73.9%) patients who underwent insertion of IPG were satisfied and using the device at last follow-up (mean 29.1 months), this suggests durability of effect and satisfaction. The two adverse events noted in this series were one patient who developed a rash after their third BTXA treatment, and another who had an anaphylactic-type reaction post-operatively. It is not known whether the BTXA was the causative etiology for these events.

Limitations to this study are relatively small patient numbers, though this does represent the largest series published to date that we know of, specifically examining SNM after prior BTXA treatment. It remains possible that with larger patient numbers, the efficacy of SNM in cases of BTXA failures may prove inferior to those in BTXA-naïve patients. As with any retrospective study, the findings are reliant on the retrospective review of data. The mean follow-up duration of 29.1 months (minimum 12 months) is adequate to establish short and medium term durability of effect, though we are not able to answer the question of long-term success from this cohort of patients at this time. Future prospective studies, with detailed patient characteristics, will be essential in helping to predict those who are most likely to respond to SNM and reduce treatment failures. While three

patients have required surgical revision in this series, it should not be forgotten that with increasing follow-up duration, an increasing percentage of patients are likely to need revision.

While the question of whether SNM or BTXA is the preferred third line option after failing conservative and medical therapy remains open to debate, it is likely that an individualized approach is most prudent. There remains no level I evidence to guide the clinician on the preferred third-line treatment modality.¹⁵ While both BTXA and SNM have their relative benefits and drawbacks, there remains a subset of patients who may fail BTXA therapy due to either lack of efficacy, urinary retention, or adverse reaction, and are appropriate for SNM treatment.

5 | CONCLUSION

As experience with BTXA grows, there is likely to be a growing number of patients who have failed first-line, second-line, and third-line (BTXA) treatments that may be candidates for SNM.

Our series demonstrates that SNM is a reasonable next step in the treatment algorithm for those with refractory OAB that have failed BTXA.

POTENTIAL CONFLICTS OF INTEREST

Dr Hoag has nothing to disclose; Dr Plagakis has nothing to disclose; Dr Pillay reports personal fees from Medtronic, personal fees from Allergan, other from Astellas, outside of submitted work; Dr Wilson Edwards reports personal fees from Allergan, personal fees and other from Astellas, personal fees from Analytica, outside of submitted work; Dr Gani reports personal fees from Medtronic, other from Astellas, outside of submitted work.

REFERENCES

1. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int*. 2001;87:760–766.
2. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20:327–336.
3. Gormley AE, Lightner DJ, Faraday M, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. *J Urol*. 2015;193:1572–1580.
4. Mangera A, Andersson KE, Apostolidis A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of Botox (onabotulinumtoxinA) and Dysport (abobotulinumtoxinA). *Eur Urol*. 2011;60:784–795.
5. Dowson C, Watkins J, Khan MS, Dasgupta P, Sahai A. Repeated Botulinum Toxin Type A injections for refractory overactive bladder: medium-term outcomes, safety profile, and discontinuation rates. *Eur Urol*. 2012;61:834–839.

6. Siddiqui NY, Wu JM, Amundsen CL. Efficacy and adverse events of sacral neuromodulation for overactive bladder: a systematic review. *Neurourol Urodyn*. 2010;29:S18–S23.
7. Banakhar MA, Al-Shaiji T, Hassouna M. Sacral neuromodulation and refractory overactive bladder: an emerging tool for an old problem. *Ther Adv Urol*. 2012;4:179–185.
8. Smits MAC, Oerlemans D, Macelissen TAT, Van Kerrebroeck PEV, De Wachter SGG. Sacral neuromodulation in patients with idiopathic overactive bladder after initial botulinum toxin therapy. *J Urol*. 2013;190:2148–2152.
9. Hossack T, Woo H. Validation of a patient reported outcome questionnaire for assessing success of endoscopic prostatectomy. *Prostate Int*. 2014;2:182–187.
10. Wagg A, Franks B, Ramos B, Berner T. Persistence and adherence with the new beta-3 receptor agonist, mirabegron, versus anti-muscarinics in overactive bladder: early experience in Canada. *Can Urol Assoc J*. 2015;9:343–350.
11. Pindoria N, Malde S, Nowers J, Taylor C, Kelleher C, Sahai A. Persistence with mirabegron therapy for overactive bladder: a real life experience. *Neurourol Urodyn*. 2015; doi: 10.1002/nau.22943 [Epub ahead of print].
12. Siegel S, Noblett K, Mangel J, et al. Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. *Neurourol Urodyn*. 2015;34:224–230.
13. Peeters K, Sahai A, De Ridder D, Van Der Aa F. Long-term follow-up of sacral neuromodulation for lower urinary tract dysfunction. *BJU Int*. 2014;113:789–794.
14. Brazzelli M, Murray A, Fraser C. Efficacy and safety of sacral nerve stimulation for urinary urge incontinence: a systematic review. *J Urol*. 2006;175:835–841.
15. Laviana A, Jellison F, Kim J. Sacral neuromodulation for refractory overactive bladder, interstitial cystitis, and painful bladder syndrome. *Neurosurg Clin N Am*. 2014;25:33–46.