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Sacral neuromodulation in patients with refractory overactive bladder symptoms after failed Botulinum toxin therapy: Results in a large cohort of patients

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Abstract

Aims: Sacral neuromodulation (SNM) and Botulinum toxin A (BoNT-A) injections are well-known third-line treatment options in patients with refractory overactive bladder (OAB). Our aim is to evaluate the success rate of SNM in patients who received prior therapy with BoNT-A injections.

Methods: All patients with OAB symptoms referred for SNM between 2006 and 2019 were included. History taking and 3-day voiding diaries assessed the complaints and suitability for SNM. The success rate of SNM in patients who received prior BoNT-A was compared with BoNT-A naive patients. Success was defined as an improvement of 50% or greater in voiding diary parameters. Satisfaction was registered at their most recent visit.

Results: A total of 263 patients underwent SNM test stimulation, of which 75 (16 male/57 female) received prior BoNT-A and 188 (46 male/142 female) were BoNT-A naive. Success rate for SNM in BoNT-A naive patients was 72.9% and in BoNT-A patients 66.7% ($p = 0.316$). Success rate after ≤2 BoNT-A injections was 68.5%, compared to 61.1% after ≥3 injections ($p > 0.05$). Success rate in patients perceiving lack of efficacy of BoNT-A was 67.4% ($p > 0.05$), subjected to temporary CISC was 73.7% ($p > 0.05$) and with temporary effect of BoNT-A was 50% ($p > 0.05$). In 86% of BoNT-A patients the system was still activated and used to their satisfaction at their last follow-up visit (mean FU, 40.70 months).

Conclusion: SNM in patients with refractory OAB who failed prior BoNT-A is an excellent approach. The number of injections nor reason of BoNT-A discontinuation have predictive value for success with SNM.

KEYWORDS
Botulinum toxin, OAB, overactive bladder, sacral neuromodulation, SNM

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1 | INTRODUCTION

The International Continence Society (ICS) has defined the overactive bladder symptom complex (OAB) as a storage symptom syndrome characterized by "urgency, with or without urgency urinary incontinence, usually associated with increased daytime frequency and nocturia".[1] OAB is a prevalent pathology with a significant impact on patient's health-related quality of life.[2,3] The prevalence of OAB in Western civilization currently is between 11.8% and 16.6% and expectations are that these numbers will only further increase due to an aging and expanding population. The burden of OAB on healthcare systems worldwide therefore is expected to rise accordingly.[4,5]

The optimal treatment algorithm for OAB still remains subject of discussion largely due to the complex (and often unknown) pathophysiology and the possible multifactorial etiology of OAB.[6–8] Current guidelines suggest a linear step-up treatment pathway with behavioral therapy including bladder training, pelvic floor muscle training, and fluid management, as initial treatment.[7,9] Pharmacotherapy is considered second-line treatment for OAB with an anti-muscarinic or a β3-agonist at our disposal.[6] However, conservative treatments often prove to be insufficient due to unsatisfactory response and intolerability. Pelvic floor muscle therapy, for instance, requires perseverance and therapy compliance to maintain effectiveness.[10] The same applies to oral therapy with an anti-muscarinic or a β3-agonist which is frequently discontinued due to limited efficacy and side-effects.[11,12] After failure of conservative measures, three minimally invasive surgical interventions need to be considered. These third-line surgical options consist of: intravesical injections with Botulinum toxin type A (BoNT-A), percutaneous tibial nerve stimulation (PTNS), and sacral neuromodulation (SNM). The guidelines do not recommend a preferred option, given the comparable efficacy of all three tertiary treatment modalities. Therefore, treatment selection currently depends on multiple factors including patient preference, surgical expertise, available resources, and financial considerations.[7] Guidelines also do not elaborate on what to do when treatment with one of these third-line options fails. While literature is sparce on this subject, Marcelissen et al.[7] recommended to attempt a switch to another third-line treatment. The patients in this study undergo SNM rather than PTNS after prior BoNT-A. This choice is based upon the long-term success rate of SNM being between 67% and 82% and the patient's desire of a permanent solution for their symptoms.[13,14]

The primary objective of the current study is to confirm the efficacy of SNM in patients with refractory OAB who received prior BoNT-A treatment. The secondary objective is to determine whether the number of BoNT-A injections and/or the reason for discontinuation of the initial BoNT-A treatment has predictive value for future SNM success.

2 | MATERIALS AND METHODS

For this observational study, all patients with OAB symptoms referred to our center for SNM between 2006 and 2019 were included and data were collected. Patients were evaluated on an outpatient basis to determine their suitability for SNM. The minimum interval between last BoNT-A and SNM was 6 months in all patients. Complaints were assessed by history taking and 3-day voiding diaries. Also, thorough evaluation of previous diagnostic procedures (cystoscopy and urodynamics) was done and when necessary repeated or added to the diagnostic set.

All suitable patients underwent SNM test stimulation, either by using percutaneous nerve evaluation (PNE) first, followed by a full or two-staged tined lead procedure (TLP) or directly by a two-staged TLP (up until 2012 PNE was commonly used in our center before switching to two-staged TLP evaluation altogether). The TLP, performed under local or general anesthesia, consisted of the placement of an unilateral tined lead into the third sacral foramen, either left or right. During the test phase patients were requested to fill out another 3-day voiding diary to compare to baseline and evaluate the effect of SNM therapy on their symptoms. The voiding diary parameters used for comparison were frequency, urgency, voided volume, and number of incontinence episodes. Success was defined as an improvement of 50% or greater in at least one of the most clinically relevant symptoms. After successful test stimulation an implantable pulse generator (IPG), being either an Interstim I or II (Medtronic), was implanted during the second procedure. In case of an unsuccessful test phase the lead was removed.

The standard postoperative care consisted of a first visit three months after implantation of the IPG, followed by annual visits at our outpatient clinic. At these routine annual visits patient's IPG was checked for technical defects, life expectancy, stimulation levels, and if necessary, reprogramming was done. The patient's satisfaction with the effect of stimulation on their OAB symptoms, was also registered at their most recent visit. All data was collected, and statistical analysis was performed using StataCorp Stata and IBM SPSS Statistics, version 27.

3 | RESULTS

Between 2006 and 2019 a total of 263 patients underwent SNM for refractory OAB at our center, of which 75 patients (16 male/57 female) received prior BoNT-A treatment and 188 patients (46 male/142 female) were BoNT-A naive. The etiology of their symptoms was of an idiopathic nature, except for 2 patients (2.6%) in the BoNT-A population and 10 patients (5.3%) in the BoNT-A naive group with a stable neurogenic disorder. An overview of patient's characteristics can be found in Table 1. The only significant difference between the two groups was seen in the type of incontinence reported at baseline and whether a urodynamic investigation was performed before SNM. No other statistically significant differences in demographic parameters were reported between the two groups of patients.

The mean number of prior BoNT-A injection sessions per patient was 1.85 with a range of 1–6 subsequent BoNT-A treatments. The dosages of BoNT-A used, varied from 100 to 300 units of onabotulinumtoxin A (Botox; Allergan Pharmaceuticals), up to 500 units of abobotulinumtoxin A (Dysport, Ipsen Biopharm Ltd). The reason for BoNT-A discontinuation in 46/75 patients (61,3%)

TABLE 1 Summary of patient demographics and treatment information

	BoNT-A	BoNT-A naive	*p* value
Included patients	75/263	188/263	-
Gender	16 male/57 female	46 male/142 female	0.589
	21.3%/78.7%	24.5%/75.5%	
Age at TLP	Mean 56.23 (18–86)	Mean 54.84 (18–79)	0.466
	Median 58.00	Median 58.00	
Etiology of incontinence			0.003
UUI	43/75 (57.3%)	98/188 (52.1%)	
SUI	0/75 (0.0%)	4/188 (2.1%)	
MUI	15/75 (20.0%)	69/188 (36.7%)	
No	17/75 (22.7%)	17/188 (9.0%)	
Urodynamics (UDS)			0.016
Yes	59/75 (78.7%)	119/188 (63.3%)	
No	16/75 (21.3%)	69/188 (36.7%)	
DO on UDS			0.264
Yes	38/59 (64.4%)	66/119 (55.5%)	
No	21/59 (35.6%)	53/119 (44.5%)	
TLP success	50/75 (66.7%)	137/188 (72.9%)	0.316
Etiology of TLP success			0.104
>50% urgency + UI	63.6%	76.6%	
<50% + subjective	6.1%%	6.4%%	
Freq. + voided V	30.3%	17.0%	
Long term success	43/50 (86%)	115/137 (83.9%)	0.443
IPG reprogramming			0.919
0	19/50 (38.0%)	40/137 (29.2%)	
1–3 times	23/50 (46.0%)	79/137 (57.6%)	
≥3 times	8/50 (16.0%)	18/137 (13.2%)	

Abbreviations: DO, detrusor overactivity; MUI, mixed urinary incontinence; SUI, stress urinary incontinence; UUI, urgency urinary incontinence; >50% urgency + UI, success based on 50% improvement in urgency and urinary incontinence; <50% + subjective, success based on improvements in urgency and urinary incontinence between 40% and 50% with subjective factors taken into account; Freq. + voided V, success based on frequency and voided volume.

was lack of efficacy after the first or subsequent injections. In 19/75 patients (25.3%) the need for temporary clean intermittent self-catheterization (CISC) was reported as the main reason for discontinuation. In total 10 out of 75 patients (13.3%) were dissatisfied with the transient effect of the treatment and the need for repeated injections. The median time interval between the first and last BoNT-A treatment was 17.50 months (min. 1–max. 121), and from the first BoNT-A injection session to SNM test stimulation 27.00 months (min. 6–max. 132). The median time interval between the last BoNT-A treatment and SNM test stimulation was 15.00 months (min. 6–max. 102).

The success rate for SNM test stimulation in BoNT-A naive patients was 72.9% (137/188) and in patients with prior BoNT-A treatment 66.7% (50/75). In 63.6% of the BoNT-A patients, success was based solely on more than 50% improvement in urgency and urinary incontinence, compared to 76.6% in BoNT-A naive patients. In 6.1% and 6.4% respectively of these populations, subjective factors were given decisive importance despite the presence of a somewhat lower than 50% (between 40% and 50%) objective improvement. More than 50% improvement in frequency and voided volume were the decisive factor in 30.3% of BoNT-A patients and 17.0% of BoNT-A naive patients. In the subset of patients that perceived lack of efficacy of BoNT-A, the success rate of SNM test stimulation was 67.4% (31/46; $p > 0.05$). However, in patients previously subjected to temporary CISC after BoNT-A the success rate was 73.7% (14/19; $p > 0.05$) and in patients with temporary effect of BoNT-A 50% (5/10; $p > 0.05$). Taken into account the number of BoNT-A injection sessions, the SNM success rate of patients receiving two or fewer BoNT-A treatment was 68.5% (37/54), compared to 61.1% (11/18) in patients with three, or more treatment sessions ($p > 0.05$). In three patients the exact number of BoNT-A treatments was unknown.

Of the 50 patients that received prior BoNT-A treatment and had a successful SNM test stimulation, 86% (43/50) were still satisfied and using the IPG at their last follow-up visit (mean FU, 40.70 months) compared to 83.9% (115/137) in the BoNT-A naive patients (mean FU, 54.18 months). This means the overall success rate of SNM in the BoNT-A population is 57.3% (43/75) and 61.2% (115/188) in BoNT-A naive patients. To date, 50 patients required IPG replacement due to IPG depletion and 30 IPG-pocket revisions were performed based on pain at IPG implant site in the total population of 188 patients. Five BoNT-A patients (10%) had their IPG explanted. Reason of explantation in two patients was pain at IPG implantation site and in three patients a urinary diversion was performed, in two for an oncological indication and in one for persistent urinary problems. Fourteen BoNT-A naive patients (10%) required explantation of their SNM system. Three patients due to infection of the SNM system. Eleven patients requested explant due to the lack of effect on their symptoms.

4 | DISCUSSION

To date there are only a few studies that evaluated the efficacy of sequential use of BoNT-A and SNM in patients with refractory OAB. There is still skepticism surrounding SNM as a treatment option, especially following prior BoNT-A. To change this perspective, studies with larger populations and long-term follow-up are needed. Our center, being a tertiary referral center for functional urology with 30 years of experience in the field of SNM, has been systematically collecting prospective data on patients receiving SNM over the years for this exact reason. In our study, the success rate of SNM after previous BoNT-A in 75 patients was 66.7% compared to a success rate of 72.9% in 188 OAB patients without previous BoNT-A treatment. The success rate in our BoNT-A naive population is in line with the high success percentages of large previous studies, adding to the representability of our results and showing the expertise in the field of SNM. Smits et al.[15] included 20 patients that received prior BoNT-A. They report a successful test phase in 14 patients (70%) and 11 patients (79%) still satisfied with the results after 1 year. Hoag et al.[16] identified 36 patients with prior BoNT-A treatment. Twenty-three patients had a successful test phase and received an IPG. At last follow-up, 17 patients (73.9%) were still satisfied. The combination of these results with our data further corroborates the hypothesis that previous BoNT-A does not affect the success of SNM. To minimize the residual effects of BoNT-A, a time-interval of 6 to 12 months between the last BoNT-A injection and SNM test stimulation is deemed necessary. In our study, the median time-interval is 15 months with 6 months being the shortest. The difference in the location of action between BoNT-A and SNM also suggests that previous treatment with BoNT-A, should not affect the success rate of subsequent treatment with SNM, and vice versa. In literature, the recent study by Baron et al.[17] confirms BoNT-A can be used in SNM non-responders, although a higher BoNT-A discontinuation rate was reported at long-term follow-up. Trinh et al.[18] also concludes BoNT-A after failed SNM remains an option but showed lower success rate compared to patients without prior SNM.

These findings may indicate that some patients are more prone to respond to either BoNT-A or SNM.

We hypothesize that a patient with third-line treatment failure potentially suffers from a more severe form of OAB or that we are witnessing a certain kind of subtype/phenotype of OAB. Therefore, our secondary objective was to determine predictive factors for the success of SNM after prior BoNT-A, to identify these specific patients. Unfortunately, we found no differences based upon the number of BoNT-A injections and the reason for BoNT-A discontinuation. However, identification of these specific patient characteristics or predictive factors would be useful, to make well based recommendations about preferred treatment options.

This study represents the largest cohort of patients to date, focusing on SNM after prior BoNT-A treatment. Although the data presented were collected in a prospective fashion, the retrospective analysis as presented in this article, is the main limitation in this study and may have created some bias. In addition, patient's subjective satisfaction with the effect of SNM was registered at their last visit. Preferably, satisfaction is measured objectively through repeated voiding diaries and/or PROMs. Mainly because SNM is a last resort therapy option in this specific patient population making the possibility of bias more probable. Although, the mainly subjective effect of SNM was registered. The very high percentage of therapy continuation confirms the positive effect as perceived by these patients.

The optimal treatment algorithm for OAB still remains subject of discussion. However, the results of this study indicate in our view that the use of SNM as a "fourth-line" treatment option after failed treatment with BoNT-A is justified. Unfortunately, we could not identify the predictive factors for SNM treatment success, hence preselection of patients is not possible on clinical parameters and a SNM test stimulation remains the only predictor of success for SNM. The results of prospective studies comparing the clinical efficacy of SNM versus BoNT-A in patients with treatment resistant OAB will allow for an evidence-based approach as a preferred third-line treatment option in refractory OAB. This evidence could influence the place of either SNM and BoNT-A in the algorithm for resistant OAB and will have an effect on future fourth line therapy.

5 | CONCLUSIONS

This study confirms the clinical efficacy of SNM in patients with refractory OAB who received prior BoNT-A injections and justifies the use of SNM as a fourth-line treatment option. Both the number of injections sessions and the reason of BoNT-A discontinuation had no effect on the success rate of SNM. The specific patient characteristics, needed to predict the a priori chance of success of either BoNT-A or SNM in patients with refractory OAB, are still not identified. Therefore, a definite recommendation for a preferred third-line treatment is still not possible but could potentially be influenced by the possibility of SNM as an efficient fourth-line option.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Data collection: Mathias Reekmans and Janine M. W. Janssen. *Statistical analysis*: Mathias Reekmans. *Study conception and design, interpretation of results, drafting & critical revision of article, and final approval of published version*: all authors.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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