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CLINICAL ARTICLE

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Sacral neuromodulation in patients with detrusor underactivity: Is biological sex an indicator?

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Abstract

Objectives: This study aimed to report sacral neuromodulation (SNM) outcomes in detrusor underactivity (DU).

Methods: A multicentric, multinational, retrospective case series was conducted between March 2017 and June 2021 in three different referral centers. Initial test phase stimulation included either a percutaneous nerve evaluation (PNE) or an advanced lead evaluation test phase (ALTP) before permanent SNM implantation. The test phases were performed under local anesthesia, either in the outpatient (PNE) or operating room (ALTP), in the prone position, which was implanted in the third or fourth sacral foramina under fluoroscopic guidance. Patients with favorable response to the initial test phase during the first 2 weeks underwent the implantable pulse generator (IPG) implantation (Medtronic neurostimulation generator device InterStim™). Favorable response was defined as ≥ 50% improvement in symptoms, frequency of clean intermittent catheterization (CIC) and/or decrease in postvoid residual (PVR), increase in voided volume, or improvement in bladder voiding efficiency (BVE) based on the bladder diary.

Results: Fifty-eight patients were recruited with a mean age of 39.95 ± 15.28 years. Among the 58 cases, 36 (62.1%) patients responded to the initial stage. Of these, 12 patients (30.8%) with non-neurogenic etiology and nine patients (52.9%) with neurologic etiology did not respond to the initial test phase; thus, they did not undergo full implantation ($p = 0.141$). Voided volume, PVR, and the median maximum flow rate (Qmax) improved significantly ($p < 0.001$) in both sexes; however, there was no statistical difference between both genders. Most female cases (78.3%), and nearly half of the men (51.4%), responded to the test phase and were candidates for the IPG phase. Among the 35 cases who underwent IPG, 27 patients (72.2% of males, and 77.8% of females; $p = 0.700$) had a favorable response to IPG. 46.6% of patients had a successful outcome at the end of the study.

Conclusion: This multicentric study showed that SNM effectively and safely provided symptom improvement in refractory DU in males similar to females which is an important finding as previously it has been suggested that SNM works better in nonobstructive urinary retention in women and not in men.

KEYWORDS
detrusor underactivity, outcome, sacral neuromodulation, underactive bladder

1 | INTRODUCTION

Underactive bladder (UAB) is a common urological condition that has recently attracted considerable scholarly attention. Due to the lack of an accurate definition, diagnostic criteria, and its overlapping symptoms with bladder outlet obstruction (BOO) and overactive bladder (OAB), detrusor underactivity (DU) has been misdiagnosed for years.[1] UAB is a clinical term characterized by low stream urine, hesitancy, intermittency, straining, and incomplete emptying while DU is a urodynamic-based diagnosis. The International Continence Society (ICS) defines DU as "a diagnosis based on urodynamic investigations, generally (but not always) with relevant symptoms and signs, manifest by low detrusor pressure or short detrusor contraction in combination with a low urine flow rate resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span (a high post-void residual may be present)."[2] Forty-eight percent of men older than 70 years and 45% of elderly women without neurologic disorders who undergo urodynamic studies for evaluation of lower urinary tract symptoms (LUTS), suffer from DU.[3]

Etiology of DU can be caused by the dysfunction of responsible factors in generating an adequate detrusor contraction. This includes myogenic failure of detrusor muscle or neurogenic failure of various nerves involved in the micturition cycle[3] such as in diabetes mellitus, bladder outflow obstruction, neurologic disorders (acute cerebrovascular accidents, multiple sclerosis, Parkinson disease, injury to the spinal cord, cauda equina, and pelvic plexus), pelvic surgery, pelvic and sacral fractures, herniated disc, lesions of the pudendal nerve, neurosyphilis (tabes dorsalis), and Guillain–Barré syndrome. Hence, predominant manifestations of DU include voiding symptoms (such as hesitancy, low stream urine, etc.) and to a lesser extent, storage symptoms.[4,5]

Although some noninvasive methods like PVR, bladder voiding efficiency, and flow rate are useful in identifying suspected DU, however, they cannot definitively distinguish DU from BOO. Proper diagnosis of DU requires that a urodynamic study is carried out. Despite this, there are no validated urodynamic criteria available to confirm DU, especially in women. Urodynamic values are also different between males and females.[3]

Treatment options for DU are classified as conservative, medical, and surgical. They all focus on reducing the complications of poor bladder emptying such as recurrent urinary tract infection, overflow incontinence, bladder stone formation, renal impairment, bothersome LUTS, decreased quality of life, and pelvic organ prolapse or inguinal hernia due to chronic straining.

Behavioral modifications include timed voiding, double voiding, pelvic floor physiotherapy, biofeedback, and clean intermittent catheterization (CIC).[1] Medical treatments (parasympathomimetics, alpha-antagonists, prostaglandin E2) have shown a limited beneficial effect.[5] Surgical therapeutic options include Botulinum toxin injection into the external sphincter, transurethral resection of the prostate, reduction cystoplasty, latissimus dorsi detrusor myoplasty, or transurethral incision of the bladder neck in women.[3,6] These methods are, however, associated with incomplete recovery or failing to improve voiding function[5] and are often innefective. Sacral neuromodulation (SNM) shows great promise as an efficient treatment in DU. SNM is proven to be a safe, and minimally invasive surgical treatment option in patients with refractory LUTS, with an approximately 80% success rate.[7] SNM was approved by the Food and Drug Administration (FDA) in 1997 and has been licensed in patients with OAB syndrome, fecal incontinence, and[8,9] chronic nonobstructive urinary retention (NOUR, refers to a condition of an inability to empty the bladder without anatomical or functional bladder outflow obstruction).[10] Although the SNM mechanism of action is unclear, the current hypothesis is that SNM modulates optimal nerve communications which are involved in the voiding reflex, by activating bladder afferent signals and inhibiting urethral afferent signals at the level of sacral spinal cord, consequently leading to regulation of forebrain structures that are involved in the consciousness of the bladder sensation, thus, normalizing bladder, bowel, and sexual function.[11] Due to the lack of comprehensive studies to evaluate the efficacy of SNM in DU, especially in men, this study aimed to report the outcomes of SNM in DU based on gender subgroup analysis.

2 | MATERIALS AND METHODS

This multicentric, multinational, retrospective case series was conducted between March 2017 and June 2021 in three different tertiary referral functional urology centers. Local institutional board permission was gained. Patients who

suffered from refractory DU (failed conservative therapies including lifestyle modifications and pharmacological treatment) were enrolled in this investigation.

2.1 | Eligibility criteria

Inclusion criteria included adults over 18 years with a urodynamic-based diagnosis of DU and symptom duration of more than 6 months who failed to respond to first and second-line treatment options. Pregnant women or those who planned to get pregnant, patients with cognitive disabilities, concomitant pelvic organ prolapse, bladder outflow obstruction index (BOOI: pdetQmax-$2 \times$ Qmax > 40 in males,[12] and probability of BOO in females = pdetQmax $- 2.2 \times$ Qmax > 18 has $> 90\%$ probability of being obstructed),[13] and patients who had any contraindication for SNM were excluded.

Although, there are no globally accepted urodynamic values for defining DU, for the purposes of confirming DU diagnosis by urodynamic, we considered DU as having the following bladder contractility Index: BCI = pdetQmax + 5 $\times$ Qmax < 100 for males[12] and pdetQmax + Qmax < 30 for females.[14] In addition, we considered bladder voiding efficacy (BVE: voided volume/[PVR + voided volume] $\times$ 100) less than 90% as underactive detrusor.[12]

We categorized the patients based on the ability of voiding into two groups, including voiders (patients who could void ≥ 50 ml), and nonvoiders (patients who could not void or can void < 50 ml). According to the ICS glossary, we considered acontractile detrusor as: "the detrusor cannot be observed to contract (i.e., no increase in pdet) during voiding urodynamic studies resulting in failure to void. Limited voiding may occur by straining. An acontractile detrusor can be of neurogenic or non-neurogenic origin."[2]

2.2 | Study design

2.2.1 | Stage I (initial phase)

Temporary percutaneous SNM implantation with standard protocols was performed before permanent implantation as an initial test phase.

Preoperative assessment included: history-taking, physical examination, a 3-day bladder diary, PVR measurement, and urodynamic study with ICS standards.[15] Demographic and medical information were recorded. The initial trial phase was performed either in the outpatient department for the percutaneous nerve evaluation (PNE) or in the operating room for the advanced lead evaluation test phase (ALTP), under local anesthesia, in the prone position into the third or fourth sacral space under fluoroscopic guidance.

2.2.2 | Stage II (implantable pulse generator placement)

Based on the information obtained from the bladder diary, and PVR, if favorable treatment response was observed during the first 2 weeks after initial phase implantation, the second stage was performed (implantation of Medtronic neurostimulation generator device InterStim™).

Favorable response was defined as $\geq 50\%$ improvement in symptoms, CIC frequency and/or PVR, voided volume, and BVE based on the bladder diary following the initial phase.

We assessed patient-reported symptom response using the global response assessment (GRA) scale as a subjective measure of clinical outcomes. On this scale, the zero score belonged to "significantly worse," which is considered treatment failure and score 5 indicated "significantly improved," which translates into successful treatment. The rest of the scores between 2 and 4 represent "somewhat worse," "unchanged" (neither worse nor better), and "somewhat improved," respectively.

Accordingly, "significantly worse," "somewhat worse," and "unchanged" indicated treatment failure, and "somewhat improved," and "significantly improved" reflected successful treatment.

2.2.3 | Statistical analysis

SPSS statistical software version 24 (IBM SPSS Statistics, IBM Corporation) was used for statistical analysis. Data were evaluated for normality based on the Kolmogorov–Smirnov test, skewness, and kurtosis. Data were reported as mean (standard deviation, SD) or median (range). For nonparametric data, Wilcoxon rank tests were used for comparison within groups. $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics at baseline

Fifty-eight patients with refractory DU who were on CIC, met the inclusion criteria and were enrolled into the study and underwent Stage I SNM with standard protocols. The mean (SD) age of patients was 39.95 (15.28) years. More than half of the cases were males (60.3%). Although, the majority of cases had sensation of incomplete emptying ($n = 42$, 72.4%), eight patients (13.8%) had no bladder sensation, and three cases (5.2%) were on CIC, thus were unable to report whether they experienced this issue. The etiology of disease

in 39 patients (69.6%) was non-neurogenic, and the others had neurogenic cause for DU. Table 1 shows the baseline characteristics and the outcomes following therapy in all cases. Table 2 represents the results of urodynamics in the included patients.

The final analysis for the outcome of neuromodulation showed that 62.1% of the total 58 cases had a response to the initial test phase, while the rest ($n = 22$; 37.9%) did not respond to the initial phase. Our results showed that this response was predominant in females rather than male patients (78.3% vs. 51.4%; $p = 0.039$) (Table 3).

Figure 1 is the flow diagram of the progress through the stages of study.

3.2 | The outcomes of Stage I

Most female cases (78.3%), and nearly half of the men (51.4%), responded to the first stage and were a candidate for the full implant IPG phase. Among the 35 cases who underwent the IPG, 27 patients (72.2% of males, and 77.8% of females; $p = 0.700$) had a favorable response to IPG. Of the 58 cases enrolled into the study, 46.6% of patients ($n = 27$; 60.9% of females, and 37.1% of males; $p = 0.076$), had a successful SNM at the end of the study.

Overall, 36 (62.1%) patients showed a favorable response to the first stage of SNM based on our defined criteria. Thirty-one patients (12 non-neurogenic, nine neurogenic), with a mean age of 47.1 (15.5) and male predominance (77.3%), had no response to Stage I. Five patients had no bladder sensation during the urodynamic study, whereas 14 patients reported incomplete emptying sensation.

We also compared the baseline characteristics of patients who responded or did not respond to Stage I based on the gender subgroup analysis (Table 4). The results showed that age, underlying etiology of DU, baseline bladder capacity, Qmax, and GRA did not differ significantly across the groups ($p > 0.05$).

TABLE 1 Baseline characteristics ($n = 58$)

Variables	Male ($n = 35$)	Female ($n = 23$)	Total ($n = 58$)	p value
[a]Age	41.14 (16.27)	38.13 (13.80)	39.95 (15.28)	0.556[b]
Etiology				0.562[c]
Idiopathic	22 (66.7)	17 (73.9)	39 (69.6)	
Neurogenic	11 (33.3)	6 (26.1)	17 (30.4)	
[a]Symptoms duration (years)	4.0 (1.0, 30.0)	5.0 (1.0, 30.0)	4.5 (1.0, 30.0)	0.745[b]
Symptoms				
Hesitancy	18 (54.4)	17 (73.9)	35 (62.5)	0.159[c]
Sensation of incomplete emptying	26 (74.3)	16 (69.6)	42 (72.4)	0.357[c]
Frequency	6 (18.2)	7 (30.4)	13 (23.2)	0.285[c]
Urgency	5 (15.2)	2 (8.7)	7 (12.5)	0.472[c]
Contractility				**0.028**[c]
Acontractile	6 (17.1)	10 (43.5)	16 (27.6)	
UAB	29 (82.9)	13 (56.5)	42 (72.4)	
Able to void				
Voiders	21 (61.8)	11 (47.8)	32 (56.1)	0.415[c]
Nonvoiders	13 (38.2)	12 (52.2)	25 (43.9)	
[a]Follow-up (months)	5.0 (1.0, 46.0)	16.0 (1.0, 44.0)	8.0 (1.0, 46.0)	**0.037**[b]

Note: Data are presented as *n* (%). Bold values are statistically significant $p < 0.05$.

Abbreviation: UAB, underactive bladder.

[a]Mean (SD).

[b]Mann–Whitney *U*.

[c]χ^2.

TABLE 2 Urodynamic parameters in baseline and after treatment ($n = 58$)

Variables	Male	Female	Total	*p* value[a] (between-subjects)
Voided volume (ml)				
Baseline	77.50 (0.0, 394.0)	50.0 (0.0, 600.0)	75.0 (0.0, 600.0)	0.585
After treatment	160.0 (0.0, 500.0)	240.0 (0.0, 550.0)	235.0 (0.0, 550.0)	0.425
p value (within-subjects)	**<0.001**	**<0.001**	**<0.001**	
Bladder capacity (ml)				
Baseline	500.0 (200.0, 1300.0)	400.0 (250.0, 900.0)	450.0 (200.0, 1300.0)	**0.015**
After treatment	500.0 (25.0, 1000.0)	400.0 (270.0, 860.0)	420.0 (250.0, 1000.0)	0.081
p value (within-subjects)	0.245	0.242	0.908	
MCC (ml)				
Baseline	532.0 (210.0, 1220.0)	405.0 (250.0, 720.0)	500.0 (210.0, 1220.0)	0.085
After treatment	-	500.0 (472.0, 550.0)	525.0 (472.0, 640.0)	0.500
p value (within-subjects)	-	0.500	0.750	
Qmax (ml/s)				
Baseline	7.0 (0.0, 20.0)	0.3 (0.0, 13.0)	5.0 (0.0, 20.0)	0.148
After treatment	10.5 (0.0, 30.0)	17.0 (0.0, 20.0)	12.0 (0.0, 30.0)	0.331
p value (within-subjects)	**0.002**	**<0.001**	**<0.001**	
PVR (ml)				
Baseline	440.0 (200.0, 1000.0)	320.0 (150.0, 650.0)	380.0 (0.0, 1000.0)	0.261
After treatment	300.0 (0.0, 800.0)	100.0 (0.0, 600.0)	147.5 (0.0, 800.0)	0.328
p value[b] (within-subjects)	**<0.001**	**<0.001**	**<0.001**	

Note: Data are presented as median (min, max). Bold values are statistically significant $p < 0.05$.

Abbreviations: BVE, bladder voiding efficacy; MCC, maximum cystometric capacity; Qmax, maximal flow rate; PVR, postvoid residual.

[a]Mann–Whitney *U*.

[b]Wilcoxon signed ranks test.

Patients who responded to the initial ATLP underwent the second stage within a 14-day interval following the completion of Stage 1. Those who had the PNE, had the wire removed within 14 days and a full implant performed at a later date. Following Stage I, no improvement was found in the GRA compared to the baseline amounts ($p = 0.095$). The median symptoms duration was 3 years (range: 1, 30 years). In addition, no improvement was observed in urodynamic parameters, as well as PVR or voided volume ($p > 0.05$) (Table 5).

3.3 | The outcomes of Stage II

Thirty-six patients who responded to Stage I, proceeded to the second stage of SNM implantation, and were followed up postoperatively to assess treatment efficacy and device complications. Seventy-eight percent of female patients had favorable responses, whereas 72% of male patients had favorable responses (Table 6).

Voided volume had improved significantly from a median of 930.0 ml (range: 0.0–600.0) to 300.0 ml (range: 0.0–550.0) ($p < 0.001$). The median PVR was reduced from 345.0 ml (range: 0.0–1000.0) to 50 ml (range: 0.0–600.0) ($p < 0.001$), and the median Qmax increased from 6 ml/s (range: 00–0.0) to 17 ml/s (range: 0.0–30.0) ($p < 0.001$) (Table 2). We reported the treatment outcome in both stages, separately based on the sex of patients. In addition, the results of the patient's GRA results are summarized in Table 6.

3.4 | Neurogenic versus non-neurogenic patients

Non-neurogenic patients showed better response to SNM than neurogenic patients (69.6% vs. 30.4%).

TABLE 3 Endpoint outcomes ($n = 58$)

Variables	Male	Female	Total	*p* value[a]
Response to test				**0.039**
Yes	18 (51.4)	18 (78.3)	36 (62.1)	
No	17 (48.6)	5 (21.7)	22 (37.9)	
Outcome				0.076
Successful	13 (37.1)	14 (60.9)	27 (46.6)	
Unsuccessful	22 (62.9)	9 (39.1)	31 (53.4)	
Ending state				0.172
Cured	8 (22.9)	7 (30.4)	15 (25.9)	
Improved	5 (14.3)	7 (30.4)	12 (20.7)	
Unsuccessful	22 (62.9)	9 (39.1)	31 (53.4)	
GRA (baseline)				0.312
1	22 (95.7)	23 (100.0)	45 (97.8)	
2	1 (4.3)	0 (0.0)	1 (2.2)	
GRA (after treatment)				0.434
1	9 (39.1)	4 (17.4)	13 (28.3)	
2	1 (4.3)	3 (13.0)	4 (8.7)	
3	4 (17.4)	3 (13.0)	7 (15.2)	
4	4 (17.4)	6 (26.1)	10 (21.7)	
5	5 (21.7)	7 (30.4)	12 (26.1)	
p value[b] (within-subjects)	**<0.001**	**<0.001**	**<0.001**	

Note: Data are presented as *n* (%). Bold values are statistically significant $p < 0.05$.

Abbreviation: GRA, global response assessment.

[a]χ^2.

[b]Sign test.

Of the 36 cases who responded to the initial phase, 28 were non-neurogenic patients (77.8%), and 8 cases had neurogenic etiology (22.2%). Neurogenic patients consisted of patients with discopathy, myelomeningocele, and incomplete spinal cord injury. The results of Mann–Whitney *U* test showed that in patients with non-neurogenic or neurogenic DU who had favorable response to second stage SNM, there were no statistically significant differences between the baseline data for voided volume, bladder capacity, mean cystometric capacity (MCC), and PVR before the initial stage ($p > 0.05$). After treatment, non-neurogenic DU cases showed significant improvement in their urodynamic study results for voided volume, Qmax, PVR when compared to patients with neurogenic DU ($p < 0.001$). In addition, GRA of non-neurogenic cases showed a higher success rate than neurogenic cases ($p < 0.001$).

3.5 | Preimplantation voiding status and SNM outcomes

Table 7 represents the outcomes of voiders and non-voiders. Based on the results, although voiders showed favorable responses at the end of the study, it was not statistically significant ($p = 0.108$).

3.6 | Detrusor contractility status and outcome

Among 58 patients, 42 (72.4%) had DU, whereas 16 (27.6%) had acontractile detrusor.

Of all 58 cases, 21 out of 22 who had DU (95.5%), did not respond to the first phase. In addition among a total of 36 cases who underwent IPG, 21 cases had DU, and the remaining cases were acontractile (Table 4).

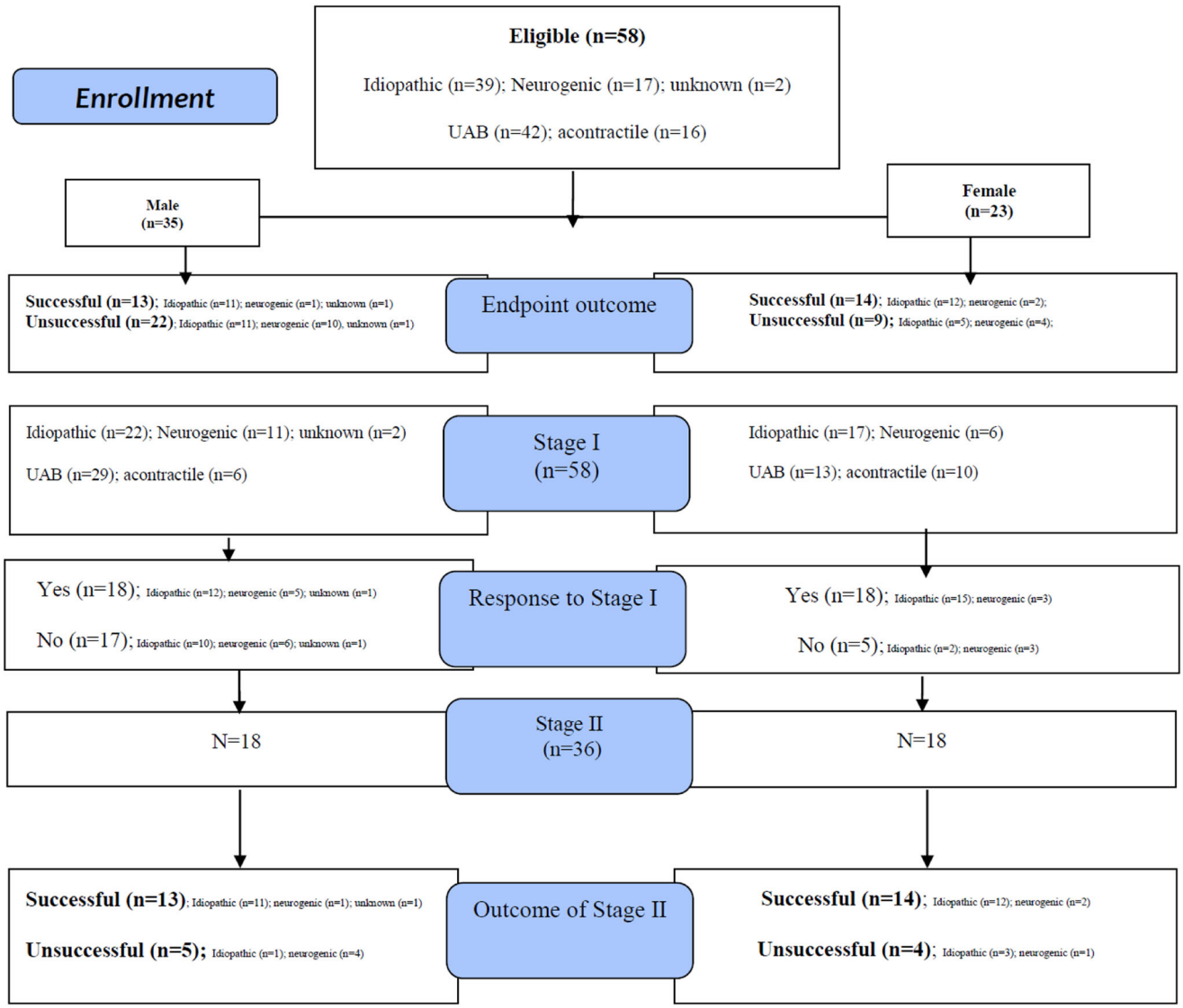

FIGURE 1 Flow diagram of the progress through the stages of study

In terms of favorable outcomes, only 9 out of 16 acontractile detrusor cases (56.3%) had favorable responses and 18 (42.9%) for DU cases.

We analyzed the data for 36 cases who responded to the test phase and underwent the second stage. Nine patients (60.0%) of the acontractile detrusor group and 85.7% of the DU group had a favorable response at the end of the study. The results of the χ^2 test showed that it was not statistically significant ($p = 0.122$).

3.7 | Adverse events

Although, no complications occurred during the initial test phase, some patients experienced device problems or adverse events in the follow-up period of second stage SNM implantation that are summarized in Figure 2.

4 | DISCUSSION

The successful effect of SNM in OAB syndrome is clear in the literature but there are limited clinical trials, assessing SNM effect in DU. This retrospective study aimed to evaluate the outcomes of SNM in patients with DU or acontractile detrusor. Our results showed that most female cases (78.3%), and nearly half of the males (51.4%), had favorable response to the first stage of SNM, of which 77.8% of females and 72.2% of males had favorable response to permanent SNM implantation. In terms of a successful outcome, 46.6% out of 58 patients (60.9% of females and 37.1% of males) had favorable response at the end of the study.

DU is a prevalent condition in men and women that has been misdiagnosed for decades due to its nonspecific LUTS and overlapping symptoms with other pathologies

TABLE 4 Baseline characteristics of responders versus non-responders to Stage I ($n = 58$)

	Nonresponders to Stage I (test phase) ($n = 22$)				Responders to stage I (implant phase) ($n = 36$)			
Variables	**Male**	**Female**	**Total**	***p* value**	**Male**	**Female**	**Total**	***p* value**
Age[a]	48.41 (16.21)	42.40 (13.39)	47.05 (15.52)	0.460[b]	34.28 (13.40)	36.94 (14.05)	35.61 (13.60)	0.564[b]
Etiology								
Idiopathic	10 (62.5)	2 (40.0)	12 (57.1)	0.611[c]	12 (70.6)	15 (83.3)	28 (77.8)	0.443[c]
Neurogenic	6 (37.5)	3 (60.0)	9 (42.9)		5 (29.4)	3 (16.7)	8 (22.2)	
Symptoms duration (year)[a]	3.0 (1.0, 6.0)	3.0 (1.0, 30.0)	3.0 (1.0, 30.0)	0.879[d]	5.0 (1.0, 30.0)	5.5 (2, 14)	5.0 (1.0, 30.0)	0.613[d]
Symptoms								
Hesitancy	6 (37.5)	3 (60.0)	9 (42.9)	0.894[e]	12 (70.6)	14 (77.8)	26 (74.3)	0.371[e]
Sensation of incomplete emptying	14 (63.6)	2 (40.0)	14 (63.6)	>0.999[e]	14 (77.8)	28 (77.8)	28 (77.8)	>0.999[e]
Frequency	1 (6.7)	0 (0.0)	1 (5.0)	>0.999[e]	5 (27.8)	7 (38.9)	12 (33.3)	0.725[e]
Urgency	2 (13.3)	0 (0.0)	2 (10.0)	>0.999[e]	3 (16.7)	2 (11.1)	5 (13.9)	>0.999[c]
Contractility				>0.999[e]				0.176[c]
Acontractile	1 (5.9)	0 (0.0)	1 (4.5)		5 (27.8)	10 (55.6)	15 (41.7)	
UAB	16 (94.1)	5 (100.0)	21 (95.5)		13 (72.2)	8 (44.4)	21 (58.3)	
Follow-up (month)[a]	1.0 (1.0, 3.0)	2.0 (1.0, 6.0)	1.0 (1.0, 6.0)	0.254[e]	11.5 (2.0, 46.0)	26.0 (2.0, 44.0)	17.5 (2.0, 46.0)	0.175[e]

Abbreviation: UAB, underactive bladder.

[a]Mean (SD)

[b]Independent samples test.

[c]χ^2.

[d]Mann–Whitney *U*.

[e]Fisher's exact test.

like BOO. In addition, coexistence of DU with BOO makes it challenging. Proper diagnosis of DU relies on urodynamic studies; however, no widely accepted urodynamic-based criteria are available for the diagnosis of DU, especially in women. Combinations of Qmax, PdetQmax, PVR, and BVE have been proposed in the literature; but there is no consensus about the cut-off of these parameters in DU. Jeong et al. assessed four different criteria which were used to indicate DU in males: BCI < 100, BOOI < 20 and Qmax < 12 ml/s, pdetQmax < 30 cmH_2O and Qmax < 10 ml/s, and BCI < 100, BOOI < 20, and bladder voiding efficiency <90%. They mentioned significant differences in the prevalence of DU by applying different criteria.[16]

With disappointing conservative and pharmacologic treatments that mainly focus on reducing residual urine to prevent subsequent sequela, with no considerable improvement in underlying pathology, SNM has created a new concept in DU treatment. SNM produces promising results in improving bladder and urethral function by optimizing nerve communications, although its mechanism of action is not yet clear. SNM has a profound impact on a patient's quality of life in a minimally invasive manner.

Chan et al., indicated that 51% of patients with DU responded to the SNM trial phase.[17] In another study, 79% of women with symptomatic chronic retention responded to SNM implantation.[13] Mehmood et al. found the efficacy of SNM in females with idiopathic NOUR was 83.3%.[7] Meng et al. showed that in cases with non-neurogenic NOUR, voiders with at least 50 ml voided volume before SNM trial had better response to SNM than patients who could not void or voided less than 50 ml.[18] Females with idiopathic NOUR could be due to Fowler's syndrome, which response very well to SNM. The high response rates mentioned in the above studies are mainly in females with retention.

In our study, 17 patients with neurogenic DU were candidates for Stage I SNM. Eight of these cases responded to the initial test phase, and 22.2% had favorable response to

TABLE 5 Urodynamic parameters in baseline and after treatment in responders versus nonresponders to Stage I ($n = 58$)

	Nonresponders to Stage I (test phase) ($n = 22$)				Responders to stage I (implant phase) ($n = 36$)			
Variables	**Male**	**Female**	**Total**	***p* value**	**Male**	**Female**	**Total**	***p* value**[a]
Voided volume (ml)								
Baseline	80.0 (0.0, 394.0)	0.0 (0.0.)	30.5 (0.0, 394.0)	**0.031**	75.0 (0.0, 370.0)	100.0 (0.0, 600.0)	93.0 (0.0, 600.0)	0.568
After treatment	0.0 (0.0, 150.0)	0.0 (0.0, 150.0)	0.0 (0.0, 150.0)	0.606	300.0 (0.0, 500.0)	295.0 (50.0, 550.0)	300.0 (0.0, 550.0)	0.905
p value (within-subjects)			0.313				**<0.001**	
Bladder capacity (ml)								
Baseline	570.0 (200.0, 1300.0)	370.0 (320.0, 700.0)	500.0 (200.0, 1300.0)	0.249	450.0 (300.0, 1186.0)	400.0 (250.0, 900)	430.0 (250.0, 1186.0)	0.095
After treatment	650.0 (350.0, 1000.0)	380.0 (330.0, 860.0)	510.0 (330.0, 1000.0)	0.06	445.0 (250.0, 700.0)	400.0 (270.0, 670.0)	400.0 (250.0, 700.0)	0.695
p value (within-subjects)			0.148				0.341	
MCC (ml)								
Baseline	536.0 (210.0, 1220.0)	505.0 (410.0, 600.0)	536.0 (210.0, 1220.0)	0.824	499.0 (250.0, 800.0)	390.0 (250.0, 720.0)	499.0 (250.0, 800.0)	0.324
After treatment	-	-	-		-	500.0 (472.0, 550.0)	525.0 (472.0, 640.0)	0.500
p value (within-subjects)	-	-	-				0.750	
Qmax (ml/s)								
Baseline	7.0 (0.0, 17.0)	-	1.0 (0.0, 17.0)	**0.031**	7.0 (0.0, 20.0)	3.5 (0.0, 13.0)	6.0 (0.0, 20.0)	0.510
After treatment	0.0 (0.0, 10.0)	0.0 (0.0, 7.0)	0.0 (0.0, 10.0)	0.518	16.0 (0.0, 30.0)	17.5 (2.0, 20.0)	17.0 (0.0, 30.0)	0.446
p value (within-subjects)			0.813				**<0.001**	
PVR (ml)								
Baseline	450.0 (0.0, 1000.0)	370.0 (320.0, 650.0)	450.0 (0.0, 1000.0)	0.401	350.0 (0.0, 1000.0)	260.5 (150.0, 650.0)	345.0 (0.0, 1000.0)	0.045
After treatment	435.0 (380.0, 800.0)	380. (330.0, 500.0)	400.0 (330.0, 800.0)	0.525	90.0 (0.0, 350.0)	50.0 (0.0, 600.0)	50.0 (0.0, 600.0)	0.845
p value[b] (within-subjects)			0.494				**<0.001**	

Data are presented as median (min, max). Bold values are statistically significant $p < 0.05$.

[a]Mann–Whitney *U*.

[b]Wilcoxon signed ranks test.

TABLE 6 Endpoint outcomes in baseline and after treatment in responders versus nonresponders to Stage I ($n = 58$)

	Nonresponders to Stage I (test phase) ($n = 22$)				Responders to Stage I (implant phase) ($n = 36$)			
Variables	**Male**	**Female**	**Total**	***p* value**	**Male**	**Female**	**Total**	***p* value**
Outcome								>0.999[a]
Successful	0 (0.0)	0 (0.0)	0 (0.0)		13 (72.2)	14 (77.8)	27 (75.0)	
Unsuccessful	17 (100.0)	5 (100.0)	22 (100.0)		5 (27.8)	4 (22.2)	9 (25.0)	
Ending state								0.835[a]
Cured	0 (0.0)	0 (0.0)	0 (0.0)		8 (44.4)	7 (38.9)	15 (41.7)	
Improved	0 (0.0)	0 (0.0)	0 (0.0)		5 (27.8)	7 (38.9)	12 (33.3)	
Unsuccessful	17 (100.0)	5 (100.0)	22 (100.0)		5 (27.8)	4 (22.2)	9 (25.0)	
GRA (baseline)								0.438[b]
1	9 (100.0)	5 (100.0)	14 (100.0)		13 (92.9)	18 (100.0)	31 (96.9)	
2	0 (0.0)	0 (0.0)	0		1 (7.1)	0 (0.0)	1 (3.1)	
GRA (after treatment)				0.095[b]				0.912[b]
1	8 (88.9)	2 (40.0)	10 (71.4)		1 (7.1)	2 (11.1)	3 (9.4)	
2	1 (11.1)	3 (60.0)	4 (28.6)		0 (0.0)	0 (0.0)	0 (0.0)	
3	0 (0.0)	0 (0.0)	0 (0.0)		4 (28.6)	3 (16.7)	7 (21.9)	
4	0 (0.0)	0 (0.0)	0 (0.0)		4 (28.6)	6 (33.3)	10 (31.3)	
5	0 (0.0)	0 (0.0)	0 (0.0)		5 (35.7)	7 (38.9)	12 (37.5)	
[c]*p* value (within-subjects)			0.125[c]				**<0.001**[c]	

Note: Bold values are statistically significant $p < 0.05$.

[a]χ^2.

[b]Fisher's exact test.

[c]Wilcoxon signed ranks test.

TABLE 7 The outcomes of SNM in voider or non-voider responders or nonresponders at the end of study

	Total			Nonresponders to Stage I (test phase) ($n = 22$)			Responders to Stage I (implant phase) ($n = 36$)		
Variables	**Favorable response**	**Unsuccessful**	***p* value**	**Favorable response**	**Unsuccessful**	***p* value**	**Favorable response**	**Unsuccessful**	***p* value**
Voiders[a]	18 (56.3)	14 (43.8)	0.108	-	11 (100.0)	-	18 (85.7)	3 (14.3)	0.112
Nonvoiders	8 (32.0)	17 (68.0)		-	11 (100.0)		8 (57.1)	6 (42.9)	

[a]Voiders (patients who could void ≥ 50 ml) and nonvoiders (patients who could not void or void <50 ml).

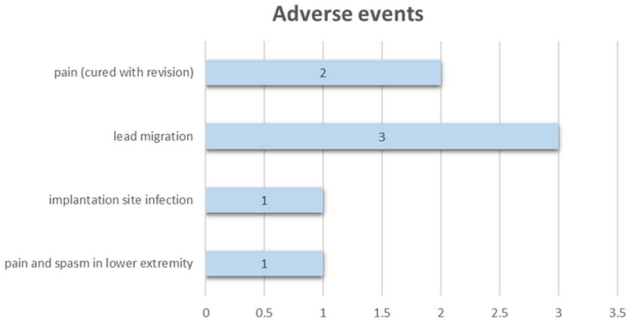

FIGURE 2 Adverse event in responders to Stage I

the permanent SNM implantation. In addition, the results showed a significant difference in the success rate after Stage II of SNM between non-neurogenic and neurogenic DU groups. Statistically, non-neurogenic DU patients responded significantly better to SNM than neurogenic patients. This difference might be due to the small number of neurogenic DU patients in the current study or either be due to the fact that with some neurogenic patients the nerve supply is affected or cannot be located accurately. Gani et al. reported that patients with neurologic DU had lower response to SNM compared with non-neurogenic patients.[10]

Moreover, we found no significant difference in response rate to SNM between the two genders, with different ages. High et al. indicated age and comorbidities like diabetes, cardiovascular disease, and chronic pain had no impact on response rate to SNM in women with DU or functional urinary retention.[19]

Chan et al. determined no difference in response rate to SNM between males and females, neurogenic and non-neurogenic, voiders (who voided with detrusor contraction or Valsalva maneuver) and nonvoiders (who could not void preimplantation). In their study, elderly patients had a lower response rate to SNM.[17]

Based on our study, voiders had better responses to SNM Stages 1and 2 than nonvoiders.

Voiders were not necessarily those who urinated by increasing detrusor pressure; they may have voided by abdominal straining instead. Voiders may have learned how to increase abdominal pressure and relax pelvic floor muscles at the same time to improve voiding efficacy.

To evaluate the success of SNM in DU, it would be more interesting to assess the pre- and postimplantation detrusor pressure, urethral pressure, and BCI. Regarding detrusor contractility status and favorable response to permanent SNM implantation, our study revealed no statistically significant difference between the acontractile detrusor group and DU group suggesting that SNM may work through urethral pressure relaxation. Due to logistical limitations, we did not perform postimplantation urodynamic studies. If we performed postimplantation urodynamics, we might have been able to evaluate the effect of SNM in DU patients, especially those with preimplantation detrusor acontractility and/or high urethral closure pressures; and see whether SNM improves detrusor contractility profile and/or relaxes the pelvic floor and external sphincter, and which response is more prominent.

Chan et al. mentioned that even patients with acontractile detrusor could respond to SNM, but the success rate was lower than others. In contrast, there was no difference between voiders and nonvoiders.[17]

Gani et al. reported that SNM implantation could be a proper treatment option in patients with DU who preserved some degree of detrusor contractility function based on preoperative urodynamics.[10]

A systematic review showed that female gender tends to be more successful in SNM.[20] To date we have no precise diagnostic criteria for voiding parameters in females, and this may be a limitation in studies that evaluate the treatment outcomes in voiding phase of females. However, in our study, male had a good response to treatment, too, and there are limited studies that investigate it, and still, there are a gap of knowledge in this issue.

Despite the promising effect of SNM in the management of DU, appropriate patient selection has the highest priority. However, it is unclear which factors could predict the success of SNM. A study suggested that NOUR patients with at least 50 ml voided volume are more likely to benefit from SNM than those who are unable to void or voided less than 50 ml.[16] Some studies mentioned that preimplantation preserved detrusor contractility was needed to get an efficacious response rate to SNM.[11]

Drossaerts et al. in their study showed that conventional UDS overestimates the amount of patients diagnosed with underactive or acontractile bladders, and patients with reduced contractility on ambulatory-UDS had a lower chance of SNM success. Hence, ambulatory-UDS allows them to select patients with real acontractile bladders and predict SNM failure. In patients with storage symptoms, additional ambulatory-UDS did not seem to contribute in predicting SNM outcome.[21]

Our main study limitation was the low number of patients in the neurogenic DU group. However, until we have a globally accepted definition for DU in men and women, larger studies may be more difficult to conduct. Although there was a lack of a sham-controlled comparative study, having men/women and neurogenic/non-neurogenic patients, meant that these groups can be compared to each other. Furthermore, we did not evaluate post-SNM implantation detrusor or urethral pressure changes, which may be considered in future prospective studies. Before choosing this approach, due to poor insurance coverage of SNM and high costs of SNM implantation shared decision-making with patients had the highest priority. Furthermore, preoperation monitoring of patients objectively and subjectively with UDS, bladder diary, PVR and questionnaires are essential.

5 | CONCLUSION

The results showed that the initial phase of SNM was successful in 62% of DU patients, of which 75% had favorable response to permanent SNM implantation. PVR, Qmax, voided volume and the patient's GRA improved after SNM implantation. The study emphasized that voided volume, PVR, and MCC can be considered as predictors of the success of SNM implantation in DU patients and useful counseling and patient selection. This multicentric follow-up study advanced the overall knowledge of SNM implantation for the treatment of DU, especially in men and neurogenic patients. The results showed that SNM effectively and safely provides relief for refractory DU in men similar to women and that men should not be denied access to a test phase of SNM if they have DU. Ultimately, the only way of knowing if SNM

will work or not, in the absence of predictive factors, is to do a test phase.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ETHICS STATEMENT

Local Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran approved the proposal: IR.TBZMED.REC.1400.534. Informed consent was obtained from all participants. Since the current study is a retrospective study, clinical trial registration is not applicable for this type of study.

AUTHOR CONTRIBUTIONS

Conceptualization and data collection: Rahmi Onur, Sakineh Hajebrahimi, Hashim Hashim, and Marie-Aimee Perrouin-Verbe. *Data curation*: Sona Tayebi, Elham Jahantabi, Changiz Naseri, and Rahmi Onur. *Formal analysis*: Hanieh Salehi-Pourmehr. *Methodology*: Sona Tayebi, Hanieh Salehi-Pourmehr, and Sakineh Hajebrahimi. *Project administration and visualization*: Sakineh Hajebrahimi. *Writing—original draft*: Sona Tayebi, Hanieh Salehi-Pourmehr, and Elham Jahantabi. *Writing—review and editing*: Rahmi Onur, Hashim Hashim, and Sakineh Hajebrahimi. All authors approved the final version of manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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