



ORIGINAL CLINICAL ARTICLE

Acute effect of sacral neuromodulation for treatment of detrusor overactivity on urodynamic parameters

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Abstract**Aim:** The aim of this study is to evaluate the acute effects of sacral neuromodulation (SNM) on various urodynamic parameters.**Methods:** Patients with overactive bladder and detrusor overactivity (DO) who were planned for percutaneous nerve evaluation (PNE) were included. Directly after the PNE, a urodynamic study (UDS) was performed. The stimulation was turned off during the first UDS (UDS 1), and during the second filling cycle, stimulation was turned on (UDS 2). The UDS was followed by a test phase of 1 week and the bladder diaries were evaluated during an outpatient clinic visit. Primary outcome measures were the differences in UDS parameter values with SNM off and on.**Results:** Ten female patients were included in the study and completed the study protocol. Eight patients showed $\geq 50\%$ improvement of symptoms following a test phase. There were no differences between UDS 1 and UDS 2 in the UDS parameters; bladder volume at first sensation, bladder volume at first DO, highest DO pressure, bladder capacity, maximum flow rate, and pressure at maximum flow rate.**Discussion:** None of the aforementioned urodynamic parameters was influenced by acute SNM in patients who responded to SNM. To the best of our knowledge, this is the first study investigating the acute effects of SNM on bladder function.**KEYWORDS**

acute effect, neuromodulation, overactive bladder, sacral root, urodynamics

1 | INTRODUCTION

Overactive bladder (OAB) is a condition defined as urgency, with or without urgency urinary incontinence, usually associated with frequency and nocturia.¹ The prevalence is described to be between 11% and 16% worldwide and is expected to increase as a result of the aging of the population causing a high burden on

society.^{2,3} The pathophysiology of this highly prevalent disease is still being explored and the value of urodynamics (UDS) in OAB is investigated. About 54.2% of patients with symptoms of OAB show detrusor overactivity (DO) on UDS.⁴

Currently, first-line treatment consists of conservative treatments like pelvic floor muscle therapy (PFMT) and second-line treatment of oral anticholinergics or

betamimetics. Neither of these treatments is very efficient. Research shows that the benefit of PFMT is not maintained on the long term and more than 50% stop anticholinergic drug treatment within the first 3 months because of lack of benefit and adverse effects.⁵

Sacral neuromodulation (SNM) is a safe and effective third-line therapy for symptoms of OAB.⁶ SNM is supposed to suppress involuntary bladder contractions and to normalize bladder sensation via afferent nerve modulation.⁷ Before implantation of a sacral neuromodulator, a percutaneous nerve evaluation (PNE) or first-stage tined lead placement test (FSTLP) is done to evaluate the efficacy in the patients with OAB. In patients with an improvement of $\geq 50\%$ of symptoms, evaluated with bladder diaries, a sacral neuromodulator is implanted.⁵

Different properties of SNM in bladder dysfunction have been investigated, such as the onset of action, the wash-out period, and the effectiveness of intermittent and on-demand SNM.⁸⁻¹¹ An argument for intermittent or on-demand SNM was a longer battery life, and, consequently, fewer surgical replacements, although the need for intermittent SNM is less urgent since the introduction of the rechargeable battery.¹² In some studies, it was found that the efficacy of SNM decreased after 5 years.¹³ Adaption by the nervous system was postulated as the cause of this.^{10,14} Other studies found that the therapeutic effect of SNM was stable after 5 to 6 years.^{6,15}

Implantable ultrasound devices and potentiometers to detect bladder filling and contractions have been studied in pigs.^{16,17} Such devices could be helpful in the development of a feedback system in which the neuromodulator automatically activates when the detrusor pressure is increasing.¹⁸ If acute SNM has direct inhibitory effects on bladder function, such a closed-loop feedback system could be of potential value for patients with OAB. Studies in rats demonstrated an acute inhibitory effect of neuromodulation on bladder contractions.¹⁹

Whether UDS parameters can predict the success of SNM in patients have been investigated, but no predictive UDS parameters have been found.^{20,21} Moreover, when comparing UDS parameters before and during SNM (6 months stimulation), several UDS parameters significantly changed; bladder volume at first sensation, bladder capacity, maximum detrusor pressure, and maximum flow rate (Qmax).²²⁻²⁴ The acute effect of SNM on UDS has never been investigated.

Therefore, the aim of this study is to evaluate the acute effect of SNM on the different UDS parameters.

2 | MATERIALS AND METHODS

The present study was approved by the local medical research ethics committee (METC 2017-471). Before the

study, written informed consent was obtained from all patients. Participation in this study was voluntary with no explicit incentives provided for participation.

2.1 | Patients

Patients with OAB and urodynamically proven DO, who were scheduled for PNE, were eligible for screening. Exclusion criteria were age under 18 years, intravesical botulinumtoxinA injections in the past 9 months, predominant stress urinary incontinence, bladder pain syndrome, neurogenic bladder, urinary tract infection, having an indwelling catheter, previous radiotherapy of the pelvis, pregnancy, and malignancies of the lower urinary tract.

2.2 | Intervention

Our standard care procedure for PNE was performed and is as follows. All anticholinergics and $\beta 3$ -adrenoceptor agonists were stopped 2 weeks before the PNE. The PNE is done in the outpatient clinic under local anesthesia. PNE's were performed using the PNE sets of Medtronic (four patients) or Axonics (six patients). A test electrode is inserted into one of the S3 foramens of the sacrum. Placement is considered correct if stimulation is felt in the vagina, penis, perineum, or anus. The electrode is then connected to the external nerve stimulator (ENS). In the current study, the patient underwent a urodynamic study (UDS 1) after placing the electrode but before the ENS was turned on. This urodynamic study was performed according to the International Continence Society criteria, using a 7-Fr transurethral double-lumen catheter and an 8-Fr rectal pressure sensor.^{25,26} The bladder filling rate was 50 mL/min. The patient was asked to indicate the first sensation of bladder filling, the first desire to void, and the moment of a strong desire to void. Permission to void was then given. Postvoid residual volume was determined through the catheter. Next, the ENS was turned on with the stimulation amplitude just above the sensory threshold and the pulse width and frequency set at 210 μ s and 14 Hz, respectively. The UDS was then repeated (UDS 2). The patients were given antibiotics for 3 days to prevent urinary tract infections following the UDS. After the UDS, the standard procedure was resumed, that is, the patient completed a bladder diary, which was evaluated after 1 week. The PNE was considered positive if at least 50% improvement was obtained in at least one of the symptoms (frequency, voided volume, or incontinence episodes). In case the PNE was inconclusive, an FSTLP was proposed in which the permanent lead is placed in one of the S3 or S4 foramens and is connected to an

external stimulator. Stimulation parameters were the same as during PNE. This test phase has a duration of about 1 month and the evaluation of success is done on the basis of bladder diary results of at least 3 days, which is comparable to the PNE evaluation.

2.3 | Outcome measures

Demographic data, data from bladder diaries and the results of the PNE and FSTLP, were extracted from the medical record (Table 1). The outcome measures were various UDS parameters as given in Table 2. The results of three different UDS were compared: UDS B (performed at baseline, before the PNE, as a part of our standard procedure of care), UDS 1 (after the PNE, without stimulation), and UDS 2 (after the PNE, with stimulation). During UDS B two filling voiding cycles were performed. Of these two cycles, the data of the filling phase with the highest filled volume and the data of the voiding phase with the highest Qmax were used in the current study.

2.4 | Statistical analysis

All statistical analyses were done with the Wilcoxon signed-rank test for nonparametric-related samples, using SPSS version 24.0 (IBM Corp, Armonk, NY).

TABLE 1 Patient characteristics

| | N |
|--|---------------|
| Male/female | 0/10 |
| Age during PNE, y, median (IQR) | 59 (54-63) |
| Frequency/24 h, median (IQR) | 13 (11-15) |
| Nocturia episodes, median (IQR) | 4 (2-6) |
| Incontinence episodes, median (IQR) | 3 (1-5) |
| Pad use/24 h, median (IQR) | 3.5 (1-5) |
| Functional bladder capacity, mL, median (IQR) ^a | 246 (125-400) |
| Overactive bladder | |
| Wet | 9 |
| Dry | 1 |
| Concomitant bladder problems | |
| Mixed incontinence | 3 |
| Therapies before PNE | |
| Pelvic floor muscle therapy ^a | 4 |
| Anticholinergics | 10 |
| TENS/PTNS ^a | 4 |
| OnabotulinumtoxinA ^a | 3 |

Abbreviations: IQR, interquartile range; PNE, percutaneous nerve evaluation; PTNS, percutaneous tibial nerve stimulation; TENS, transcutaneous electrical nerve stimulation.

^aData of one patient was incomplete.

3 | RESULTS

A total of 10 female patients with a mean age of 59 (interquartile range 54-63) years were willing to participate and completed the study protocol, see Table 1 for patient characteristics. All patients had OAB for at least 2 years with proven DO on UDS B. All patients except for one (patient 9) also showed DO during UDS 1 and UDS 2. The PNE was positive in four patients, inconclusive in four patients, and negative in two patients (patients 2 and 9). The four patients with an inconclusive result reported to feel stimulation during UDS 2 but lost sensation after 2 to 4 days, possibly due to the displacement of the lead. An FSTLP was next done, with a positive outcome in all four patients. Consequently, a permanent neuromodulator was implanted in eight patients.

The median UDS 1 and UDS 2 parameters of the positively responding eight patients are shown in Table 2. No statistically significant differences were found between UDS parameters without stimulation (UDS 1) and with stimulation (UDS 2). Figure 1 shows UDS parameters during the filling phase, three data points are shown; UDS at baseline, UDS directly after the PNE without stimulation (UDS 1), and UDS directly after PNE with stimulation (UDS 2). The lines represent the eight positively responding individuals and their median. In the outcome parameter "bladder volume at first sensation," four lines are missing. These patients did not indicate when the first sensation was notified. UDS

TABLE 2 Urodynamic parameters of UDS 1 and UDS 2

| | UDS 1 | UDS 2 | P value* |
|-----------------------------------|-----------------------|-----------------------|----------|
| Filling phase | | | |
| Bladder volume at first sensation | 157 mL | 115 mL | .854 |
| IQR | (89-290) | (63-147) | |
| Bladder volume at first DO | 184 mL | 179 mL | .263 |
| IQR | (110-300) | (125-340) | |
| Highest DO pressure | 32 cmH ₂ O | 32 cmH ₂ O | .574 |
| IQR | (21-35) | (21-35) | |
| Bladder capacity, mL | 175 mL | 190 mL | .401 |
| IQR | (79-518) | (160-364) | |
| Micturition phase | | | |
| Maximum flow rate | 12 mL/s | 10 mL/s | .462 |
| IQR | (10-17) | (6-14) | |
| Pressure at maximum flow | 31 cmH ₂ O | 31 cmH ₂ O | .089 |
| IQR | (26-43) | (27-39) | |

Abbreviations: DO, detrusor overactivity; IQR, interquartile range; UDS, urodynamic study.

*Wilcoxon signed-rank test for nonparametric-related samples.

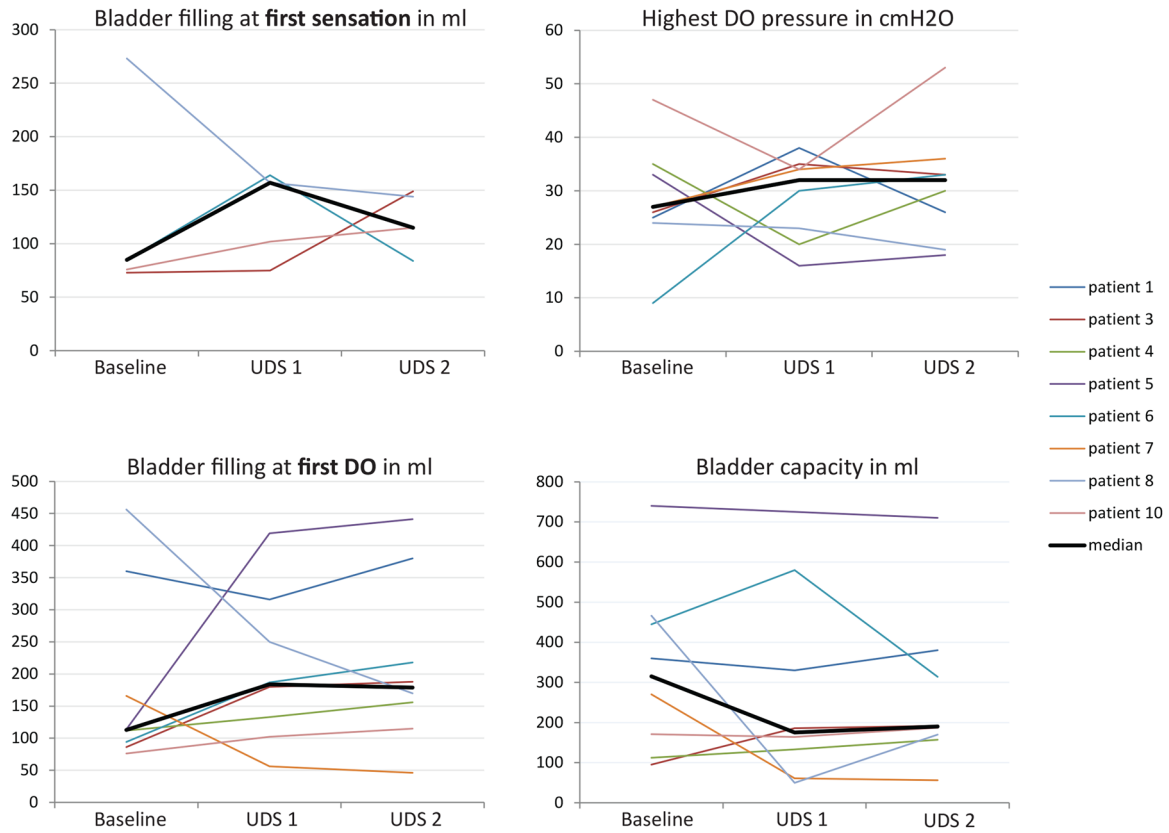


FIGURE 1 Urodynamic parameters of the filling phase of UDS B, UDS 1, and UDS 2. DO, detrusor overactivity; UDS, urodynamic study

parameters of the voiding phase are shown in Figure 2. Qmax and the pressure at maximum flow rate did not change significantly comparing UDS 1 and UDS 2, also shown in Table 2.

4 | DISCUSSION

To the best of our knowledge, this is the first study that suggests that SNM has no significant acute effect on

standard UDS parameters in patients with OAB in whom SNM is eventually an effective treatment. This accounts for both the filling phase and the voiding phase. The figures show that besides the median change of the parameters, the individual changes are also limited. These results are complementary to the results of previous studies. Significant changes in UDS parameters were demonstrated after 6 months of SNM in patients with DO for both the filling and the voiding phase; the bladder volume at first sensation increased, the bladder

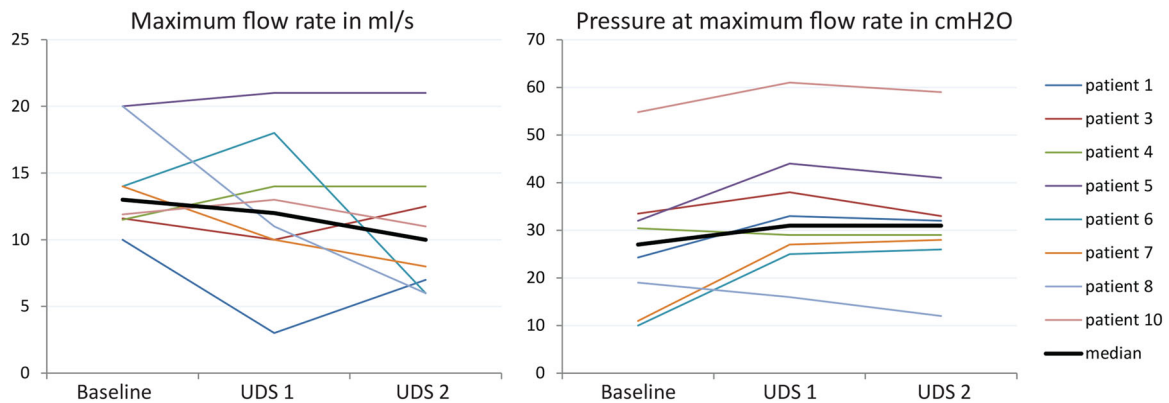


FIGURE 2 Urodynamic parameters of the voiding phase of UDS B, UDS 1, and UDS 2. UDS, urodynamic study

capacity increased, the maximum detrusor pressure during the filling phase decreased, and the Qmax increased.²²⁻²⁴

The working mechanism of SNM is still being investigated, but at present, it is believed that SNM activates afferent pathways modulating several brain areas which, in turn, regulate bladder control. Differences between acute and chronic SNM in regional cerebral blood flow (rCBF) have been demonstrated using PET.⁷ When acute SNM is applied, brain areas predominantly involved in sensorimotor control, showed an increase in rCBF. Moreover, during acute SNM, Blok et al described a change of rCBF in the insula. Blok et al⁷ argued that this might cause the activation of the sympathetic system, which, in turn, results in an increase in the bladder capacity. The bladder capacity was not measured during this PET study. The current study did not demonstrate an increase in the bladder capacity after acute SNM. In contrast to us, the study of Opisso et al did show such an increase. They used subject-controlled dorsal genital nerve stimulation in patients with neurogenic bladders due to partial spinal cord injury, multiple sclerosis, or traumatic brain injury.²⁷ Subjects could turn on the stimulator as soon as they felt urgency during bladder filling. However, the underlying mechanisms of bladder dysfunction in neurogenic and idiopathic patients are not comparable.²⁸ In the present study, only patients with idiopathic OAB were included. During chronic stimulation, when SNM has been active for 6 months, changes in the rCBF in brain areas involved in attention and alertness were detected.⁷ This, in turn, would result in less firing of the pontine micturition center and restore bladder function. The fact that this rCBF change in the brain areas involved in attention and alertness is only detected after chronic SNM and not after acute SNM might be related to the working mechanism of SNM and could explain the differences in results in UDS between acute and chronic stimulations. The areas predominantly involved in sensorimotor control showed a decrease in rCBF after chronic stimulation, instead of the increase in rCBF after acute SNM. This change might also explain the differences in results in UDS between acute and chronic stimulations. The wash-out duration of SNM has been investigated. Cadish et al⁸ found a mean of 11.25 days before the return of symptoms after turning the SNM off in 12 women with OAB. Altomare et al⁹ detected that in 19 patients with urinary incontinence or fecal incontinence, the mean time to the recurrence of symptoms after turning the SNM off was 3.4 months (range 0.9-13.5) and in nine patients symptoms never returned. In conclusion, chronic effects of SNM seem to be maintained some time after stimulation is stopped, suggesting neuroplasticity of the involved brain areas.

Moreover, the onset of action of SNM was recently investigated using bladder diaries which indicated that the mean time to 50% or greater symptom improvement was 3.3 days.²⁹

These results, and those of the current study, suggest that a closed-loop feedback system, which activates SNM automatically when the detrusor pressure increases, would not be effective due to lack of acute effects after such short stimulation. However, on-demand and intermittent neuromodulations have been proved to be effective therapies in two separate trials.^{11,14} A possible explanation might be that in both trials, the patients were already using the SNM for more than 7 years and 48 months, respectively.^{11,14} The aforementioned neuroplasticity of the involved brain areas might already have been utilized, indicating that hypothetically, these neuroplastic changes can be maintained by intermittent or on-demand neuromodulation. Suggestions for future research in the use of a feedback neuromodulation system would be to investigate it with patients who are long-term users and who are starting users of SNM.

The main limitation of the current study is its small sample size. We initially aimed at larger sample size. However, considering the absence of statistically significant findings in eight successfully tested patients and the invasiveness of the UDS, we decided to stop inclusion for ethical reasons. In four patients, the first sensation of bladder filling was not noted because they had an involuntary detrusor contraction followed by direct urine leakage and micturition. Four patients had undergone an FSTLP after the PNE because of inconclusive PNE results. This inconclusive PNE was most likely caused by lead migration as all four patients described a loss of sensation of stimulation after some days. Lead migration is a known disadvantage of PNE compared with an FSTLP and might be the cause that PNE is a less sensitive screening method than FSTLP.³⁰ In our hospital, patients with OAB first undergo a PNE, in case this is inconclusive, an FSTLP is conducted. The influence of this on our study results is considered minimal, since all four patients reported to feel stimulation during the UDS 2 at the same location as during the placement of the PNE lead. Moreover, the stimulation parameters used during PNE and FSTLP were the same (frequency 14 Hz and pulse width 210 μ s). Ultimately, for this study, it was merely of relevance whether or not the patient is a responder to SNM in general. The method of testing is of secondary importance.

In conclusion, this study suggests that there are no acute effects of SNM on conventional UDS parameters. More studies are needed to confirm this finding and further elucidate the role of factors, such as sex, age, and etiology of OAB.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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