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USE OF PERIPHERAL NEUROMODULATION OF THE S3 REGION FOR TREATMENT OF DETRUSOR OVERACTIVITY: A URODYNAMIC-BASED STUDY

H. C. KLINGLER, A. PYCHA, J. SCHMIDBAUER, AND M. MARBERGER

ABSTRACT

Objectives. To determine the efficacy of peripheral neuromodulation of the S3 region in patients with urgency-frequency syndrome due to an overactive bladder.

Methods. Fifteen patients (11 women and 4 men) with urgency-frequency syndrome, as documented by a voiding chart, were diagnosed with overactive bladder. Pelvic pain was assessed by a visual analogue scale (VAS). Full urodynamic workup was performed before and after 12 peripheral stimulations with a 9-V monopolar generator, the so-called Stoller Afferent Nerve Stimulator (SANS). Follow-up was for a mean (SD) of 10.9 (4 to 15) months.

Results. Reduction in pain was achieved in all patients, with a decrease in VAS from a mean (SD) of 7.6 (5 to 10) to 3.1 (1 to 7) ($P = 0.00049$). Seven patients (46.7%) had a complete response and were considered cured, 3 (20.0%) showed significant improvement, and 5 (33.3%) were classified as nonresponders. Urodynamic evidence of bladder instability, evident in all patients before treatment, was eliminated in 76.9% of patients. In all patients, mean (SD) total bladder capacity increased significantly from 197 (35 to 349) to 252 (78 to 384) mL ($P = 0.00795$), mean (SD) volume at first bladder sensation from 95 (16 to 174) to 133 (32 to 214) mL ($P = 0.00166$), and mean (SD) bladder volume at normal desire to void from 133 (27 to 217) to 188 (47 to 296) mL ($P = 0.00232$). In the responding group, the mean (SD) total numbers of voids was reduced from 16.1 (9 to 24) times during the day and 4.4 (2 to 6) times during the night to 8.3 (6 to 10) and 1.4 (1 to 2) times ($P = 0.002539$), respectively. No complications from treatment were observed.

Conclusions. Peripheral neuromodulation of the S3 region can successfully treat patients with urgency-frequency syndrome due to an overactive bladder. UROLOGY **56:** 766–771, 2000. © 2000, Elsevier Science Inc.

The urgency-frequency syndrome is a common clinical problem. Resnick *et al.*[1] found that 30% of the population aged over 60 years and more than 50% of residents of nursing homes had bladder control problems, in particular from an overactive bladder, as defined by the International Continence Society (ICS).[2] The main symptoms of this entity are an urgency-frequency syndrome or pelvic pain. Treatment options range from pelvic floor re-education to pharmacotherapy and invasive surgical procedures.

Electrical stimulation of the pelvic floor, termed *neuromodulation*, has been used extensively to reduce symptoms of urinary urgency or frequency or pelvic pain. The mechanism involves decreasing bladder overactivity by stimulating peripheral nerves, which represent the same spinal sacral S3 area as the bladder. Three pathways are debated: (1) at low bladder filling volumes, by direct stimulation of the hypogastric nerve through activation of the sympathetic fibers; (2) at maximal bladder filling, by direct stimulation of the nuclei of the pudendal nerve in the spinal cord; and (3) due to a supraspinal inhibition of the detrusor.[3–8] Success rates have been reported to range from 37% to 90%,[3–6] dependent on the definition of success.

Neuromodulation may be achieved through a transvaginal or transanal route[6–10] using surface electrodes These approaches, however, are not very specific. Alternatively, a more focused method would be a transcutaneous stimulation of the pure

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afferent bundles of the pudendal nerve (TENS/P),[11,12] but this technique is often too complicated for elderly patients. Another option is the implantation of a permanent sacral root nerve stimulator,[13–17] although this is a very elaborate and invasive technique.

The Stoller Afferent Nerve Stimulator (SANS; UroSurge, Coralville, Iowa) utilizes the posterior tibial nerves for transcutaneous access to the S3 spinal region.[18] We report here on experience with this new device in the treatment of patients with urgency-frequency syndrome due to an overactive bladder in a urodynamic-based study.

PATIENTS AND METHODS

A total of 15 patients (11 women and 4 men) were enrolled in this prospective study, which was approved by the local ethics committee (No. 327/98). By definition, patients with a documented daytime frequency of more than eight voids and/or a nocturia of more than two voids were regarded as having urgency-frequency syndrome. Patients underwent complete medical history, and physical and neurourologic examinations. Pelvic pain was quantified using a visual analogue scale (VAS), ranging from 0 to 10 (0 representing no pain and 10 the worst possible pain). Serum creatinine values and renal ultrasonography were obtained to exclude upper urinary tract disease. Urine culture was measured to rule out urinary tract infection. Cystoscopy with barbotage cytology was carried out to exclude malignant disease. A micturition cystogram with Valsalva maneuvers was performed in women to eliminate severe anatomic insufficiency of the pelvic floor. A standardized Pad test[19] was performed in all patients to document urinary leakage. In patients with severe bladder pain a pressure-flow study with potassium chloride (KCl) solution and a bladder biopsy were performed. Evidence for interstitial cystitis (IC) could be documented in 3 patients through mast-cell infiltration and ulceration of the bladder wall or by decreased bladder capacity and hypersensitivity during KCl pressure-flow study.

Technique

Peripheral afferent nerve stimulation was performed without local anesthesia, with the patient in a supine position.[18] Needle insertion was three-finger breadth cephalad from the medial malleolus. A 34-gauge needle was punctured through the skin and advanced approximately 4 cm, posterior to the tibia, at a 30° angle toward the ankle (Fig. 1). A ground electrocardiogram pad was placed at the same site and the needle connected to a 9-V AC monopolar generator, the SANS device. Stimulation was selected within a range of 0.5 to 10 mA, with a fixed pulse width of 200 microseconds and a frequency of 20 Hz. Proper stimulation was identified by great toe flexion and/or plantar flexion of digits two to five. Stimulation continued for 30 minutes, with 12 stimulations performed at a rate of 4 per week. Following this period, further therapy was individualized, although most responders opted to wait until symptoms re-occurred. Symptoms re-occurred in only 2 patients and they were treated with peripheral neuromodulation once every week after a primary treatment of 4 stimulations within 1 week.

Assessment

After the 12 stimulations, all baseline examinations were repeated except cystoscopy and voiding cystogram. Patients were requested to complete another voiding volume/frequency chart. A multichannel pressure-flow study[20] was performed according to ICS standards at baseline and after 12 treatments, determining total bladder capacity; volume at first bladder sensation; volume at normal desire to void; bladder compliance; maximum detrusor pressure; detrusor pressure at maximum uroflow; maximum uroflow (Qmax); and residual postvoid volume. In addition, the cough leak point pressure (CLPP) at maximal bladder capacity was evaluated. In all women, a urethral pressure profile was performed to obtain maximum urethral closing pressure, functional urethral length, and pressure transmission rate.

The success of treatment was defined according to the criteria shown in Table I.

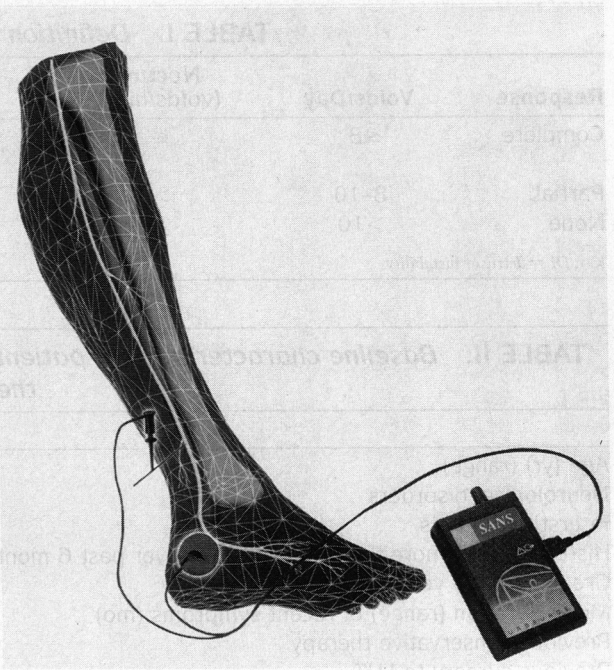


FIGURE 1. *Schematic of the site of stimulation, about three fingers' breadth cephalad of the medial aspect of the malleolus. Stimulation of the spinal S3 region is performed through the posterior tibial nerves with the Stoller Afferent Nerve Stimulator (SANS). The stimulator is attached with a connecting lead to the 34-gauge needle and a neutral surface electrode.*

Statistical Analysis

Statistical analysis was carried out using a standard software program (WinSTAT 3.1). Wilcoxon test was performed; $P < 0.05$ was considered to be statistically significant.

RESULTS

Baseline characteristics of patients are shown in Table II. Results given are means (SD). Mean total numbers of voids in the responding group (n = 10) was reduced from 16.1 (9 to 24) times daily and 4.4 (2 to 6) times during the night to 8.3 (6 to 10) and 1.4 (1 to 2) times ($P = 0.00253$), respectively. The mean number of episodes of involuntary daily urine leakage decreased from 4.1 (2 to 7) times to 2.4 (2 to 4) times daily and the mean number of

TABLE I. *Definition of response to treatment*

Response	Voids/Day	Nocturia (voids/night)	Pad Test (g)	Detrusor Instability	Subjective Response
Complete	≤8	≤2	0–1	Nonimproved or improved (asymptomatic DI)	Cured
Partial	8–10	>2	2–10	Improved	Cured
None	>10	>2	>10	Unchanged	Unchanged

KEY: DI = detrusor instability.

TABLE II. *Baseline characteristics of patients classified as responders and nonresponders to the SANS*

	Responders (n = 10)	Nonresponders (n = 5)
Age (yr) (range)	67.6 (45–92)	54.8 (40–72)
Neurological disorders	0	1 (20%)
Interstitial cystitis	1 (10%)	2 (40%)
History of UTI (more than two episodes over past 6 months)	1 (10%)	2 (40%)
Greater than 5 years' duration of disease	3 (33%)	3 (60%)
Mean duration (range) of recent symptoms (mo)	11 (5–24)	27 (8–72)
Previous conservative therapy	10 (100%)	5 (100%)
Previous surgery to LUT	3 (33%)	1 (20%)

KEY: UTI = urinary tract infection; LUT = lower urinary tract.

protective pads used per day from 4.2 (3 to 6) to 1.3 (1 to 2). According to the definition set out in Table I, a complete response was achieved in 7 patients (46.7%). Three patients (20.0%) showed significant improvement in their symptoms and subjectively regarded themselves as being cured. However, urinary frequency of eight voids or more and nocturia of two or more was demonstrated in the voiding diary of these patients. Consequently, this group was regarded as partial responders. No response was observed in 5 patients (33.3%). Two of these nonresponders, however, had IC. Another patient had peripheral neurologic disease of unknown origin.

Overall, pelvic pain, as assessed by a VAS, decreased from a mean score of 7.6 (5 to 10) to 3.1 (1 to 7) ($P = 0.0049$). VAS decreased in all but 1 patient, a nonresponder who had peripheral neurologic disease of unknown origin.

Urodynamic Assessment

Nonurodynamic results from all patients are listed in Table III. Urodynamic findings were available from only 13 patients (Table IV), as 2 patients from the nonresponder group refused to undergo further invasive testing after treatment. Detrusor instability was demonstrable in all patients before treatment but was eradicated in 9 patients after therapy and improved in 1 patient, equating to a response rate of 76.9%. Mean total bladder capacity increased from 197 (35 to 349) mL before treatment to 252 (78 to 384) mL ($P = 0.00795$) after treatment; mean volume at first bladder sensation increased from 95 (16 to 174) to 133 (32 to 214) mL ($P = 0.00166$); and mean bladder volume at normal desire to void increased from 133 (27 to 217) to 188 (47 to 296) mL ($P = 0.00232$).

The following results were recorded for the responder group (n=10); mean (SD) values are provided throughout. Total bladder capacity increased from 175 (50 to 300) to 266 (175 to 384) mL ($P = 0.00345$); bladder volume at first sensation from 96 (25 to 134) to 143 (88 to 214) mL ($P = 0.00625$); and bladder volume at normal desire to void increased from 134 (44 to 217) to 206 (169 to 296) mL ($P = 0.00345$). Qmax decreased from 14.7 (5 to 25) to 12.1 (7 to 19) mL/s and maximum detrusor pressure at peak flow from 57.2 (30 to 112) to 51.1 (27 to 82) cmH_2O. There was a decrease in the maximum detrusor pressure from 34.5 (3 to 68) to 29.4 (3 to 58) cmH_2O. No change was noted from pretreatment values in the following parameters: postvoid residual volume, bladder compliance, CLPP, and urethral pressure profile.

Side Effects

No complications were observed, besides one minor hematoma at the site of puncture. In particular, no peripheral neural damage of the posterior tibial nerve occurred during treatment or follow-up.

COMMENT

It is thought that neural stimulation of the pudendal nerve reflex loop at a frequency of 35 to 40

TABLE III. ***Nonurodynamic results before and after treatment***

Patient	Response	VAS		Pad Test (g)		Frequency (voids/day)		Nocturia (voids/night)		Average Bladder Volume (mL)		24-hr Total Urine Volume (mL)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	R	10	5	1	0	20	8	5	2	100	150	1200	1700
2	NR	7	1	83	162	15	10	3	3	100	170	2000	1600
3	NR	7	7	0	0	10	12	3	3	180	200	1880	2450
4	NR	7	4	0	0	10	9	4	3	100	140	1250	1250
5	NR	7	4	0	2	15	10	4	3	200	220	1450	1800
6	R	6	4	0	0	12	10	3	2	120	180	1240	1250
7	R	5	1	0	0	12	7	4	1	120	250	1500	1400
8	R	7	4	3	0	15	10	6	2	140	150	1540	1640
9	R	7	1	0	0	20	10	4	1	140	200	1500	1600
10	R	8	4	0	0	18	8	2	1	160	200	1200	2000
11	R	7	2	0	0	9	8	3	1	90	110	1100	1150
12	NR	8	6	25	15	12	10	2	3	150	150	1300	1500
13	R	10	1	0	0	11	6	4	1	250	350	2100	1800
14	R	8	2	0	0	24	8	5	1	90	250	1800	1500
15	R	10	4	15	9	20	8	8	2	40	150	750	1450

KEY: VAS = visual analogue scale; R = responder; NR = nonresponder.

TABLE IV. ***Urodynamic results before and after treatment for responders and nonresponders***

Patient	Response	Bladder Volume (mL)		Volume at First Sensation (mL)		Volume at Normal Desire to Void (mL)		Qmax (mL/s)		Pdet max (cmH_2O)		PdetQmax (cmH_2O)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	R	120	165	90	88	120	115	12	12	59	61	59	31
2	NR	300	186	174	180	182	172	25	19	12	27	3	3
3	NR	234	354	70	94	167	170	15	15	34	55	33	23
4	NR	349	*	106	*	104	*	14	*	87	*	66	*
5	NR	302	*	135	*	182	*	46	*	50	*	22	*
6	R	256	253	111	158	143	197	8	8	79	35	68	33
7	R	282	362	125	164	140	295	13	8	52	52	44	58
8	R	141	178	96	90	119	133	17	14	58	49	28	27
9	R	238	263	91	135	145	208	11	8	87	52	46	40
10	R	239	254	113	214	217	233	15	16	49	82	19	34
11	R	151	250	83	115	102	224	10	12	85	70	34	33
12	NR	35	78	16	32	27	47	5	7	36	74	20	21
13	R	300	318	88	116	126	169	6	17	43	38	40	21
14	R	211	384	134	174	183	296	17†	12	30	50	*	40
15	R	50	230	25	176	44	191	6	10	112	19	14	14

KEY: Qmax = maximum uroflow; Pdet max = maximum detrusor pressure; PdetQmax = detrusor pressure at Qmax; R = responders; NR = nonresponders.
* *Not available.*
† *Free uroflow.*

Hz improves reinnervation and conversion of fast into slow twitch fibers. In addition, by stimulation at 2 to 10 Hz the detrusor muscle may be affected directly, leading to reflex inhibition.[21] The SANS device utilizes a fixed stimulation at 20 Hz, which could target both sites of action. In addition, by stimulation of the posterior tibial nerves, the S3 segment can be stimulated reliably, in contrast to a more unspecific stimulation by surface electrodes.

Sacral neuromodulation, by implantation of a permanent sacral root stimulator,[14–17] stimulates the S3 region, resulting in an overall success rate of 50%[16] to 79%.[17] In the present series, 66.6% of patients were cured or at least significantly improved using a much less invasive procedure. In addition, all patients who responded well to the initial treatment were also offered an implantation of a permanent sacral root stimulator, but preference for the less invasive procedure was clearly demonstrated.

In addition, the average initial costs of a permanent implant (InterStim, Medtronic, Vienna, Austria) including surgery amounts to Euro 10290 (U.S. $8849),[22] compared with Euro 895 (U.S. $770) for the SANS device (single patient use).

Pelvic pain was a predominant symptom. This side effect was unexpected, as patients with urgency-frequency syndrome do not usually complain of excessive pelvic pain. These findings suggest that more patients may have had IC, even if no evidence of disease was detected during diagnostic workup.

A 36% reduction in urinary frequency and an increase in mean bladder capacity from 160 to 255 mL have been reported in a urodynamic study of the TENS/P.[11] These results are similar to those recorded in the present study. The SANS device may be considered slightly more invasive, but no significant complications were observed. According to our own experience, however, elderly women in particular are reluctant to use the clitoral clip electrodes in the TENS/P procedure because they are embarrassed by the technique. Likewise, many patients are not able to place the electrodes properly, resulting in reduced clinical efficacy. With the SANS device, however, selection of the proper stimulation site is very simple and can be performed by the patients themselves. Consequently, in elderly patients, the SANS device should be the first choice when considering a patient for afferent neuromodulation.

Long-lasting improvement in symptoms was achieved. This finding was remarkable, because after sacral neuromodulation, symptoms tend to recur almost instantaneously after deactivation. An explanation for this finding might be the short-term history of disease in our responding group, because patients undergoing sacral neuromodulation tend to have a long-term history of disease.

The present findings suggest that patients with symptoms related to IC in conjunction with severe structural changes in the bladder wall do not benefit from peripheral neuromodulation. However, most cases of IC are diagnosed on the basis of clinical findings only. Consequently, it should be noted that all our patients with IC in whom treatment failed had at least a 7-year history of this disease. In addition, because of untreatable urge incontinence and bladder pain 1 patient had to undergo urinary diversion. In contrast, the only patient with IC who responded with a complete remission had a short-term history (8 months) and a "normal" bladder capacity on urodynamic investigation. Overall, our findings suggest that this category of patient will benefit from SANS treatment only if significant structural changes within the bladder wall have not already occurred.

CONCLUSIONS

Use of peripheral neuromodulation with the SANS device in patients with bladder overactivity resulted in cure or significant improvement in most patients and achieved a reduction in pelvic pain in all patients. The technique is safe, resulting in no side effects. Peripheral neuromodulation is a valuable tool for the treatment of patients with urgency-frequency syndrome, consequently avoiding invasive surgery. Further data from larger patient groups are warranted to support these promising initial results.

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