

Combination of Sacral Neuromodulation and Tolterodine for Treatment of Idiopathic Overactive Bladder in Women: A Clinical Trial

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Purpose: To evaluate the efficacy of intermittent percutaneous needle sacral nerve stimulation (IPN-SNS) in women with idiopathic overactive bladder (IOAB) treated with tolterodine.

Materials and Methods: A total of 240 female patients diagnosed with IOAB were randomized to receive tolterodine only treatment (group 1, n = 120) or tolterodine combined with IPN-SNS (group 2, n = 120). Each group included 120 participants, who were divided into subgroups depending on whether they had dry OAB (urinary frequency and urgency) or wet OAB (urinary frequency and urgency with urgency incontinence). In the treatment group, patients received percutaneous IPN-SNS plus tolterodine (2 mg once daily), while in the control group, only tolterodine (2 mg once daily) was administered for 3 months. The voiding diary and urodynamic parameters were monitored, and patients' psychological depression and anxiety scores were recorded before and after treatment.

Results: There were significantly greater improvements in the conditions of first desire to void (FDV), maximum cystometric capacity (MCC), and daily average volumes, as well as the daily single maximum voided volumes in group 2 ($P = .001$) than in group 1. In addition, there were significantly greater decreases in self-rating depression scale (SDS) and self-rating anxiety scale (SAS) scores in group 2 compared with group 1 ($P < .001$).

Conclusion: Combined treatment with tolterodine plus IPN-SNS can not only improve the symptoms of voiding dysfunction but can also reduce the concomitant depression and anxiety in women with IOAB, thereby improving patients' quality of life.

Keywords: electric stimulation therapy; electrodes, implanted; urinary bladder; neurogenic; complications; overactive; therapy.

INTRODUCTION

Overactive bladder (OAB) syndrome is characterized by urinary urgency accompanied by frequency and nocturia, with or without urgent urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology.⁽¹⁾ In our country entering an era of an aging population, the incidence of diabetes mellitus, cerebral thrombosis and other neurologically damaging diseases is increasing. At the same time, there is also, a growing number of individuals affected by OAB; therefore, there is a great need to find effective treatments for OAB. Studies show that the incidence of OAB in Europe is over 17% in persons over 40 years of age, which is a higher rate than that of Alzheimer's disease and osteoporosis.⁽²⁾ While in China, the incidence of OAB in adults (> 18 years of age) is 5.2%.⁽³⁾ The pathogenesis of OAB is mainly thought to be related to idiopathic or neurogenic detrusor overactivity. Neurogenic overactivity is often caused by confirmed neurologic disease, whereas idiopathic detrusor overactivity may be due to a nonspecific infection of the bladder itself, as well as radiation cystitis, interstitial cystitis, bladder outlet obstruction, or various psychological factors. OAB in turn can lead to depression, so patients' overall quality of life may be negatively affected by the disease. Tyagi and colleagues have reported that OAB patients' social activities are largely restricted because most of them are unwilling to accept the diagnosis and undergo treatment, so they are prone to suffer from depression and anxiety.⁽⁴⁾ Antimuscarinic drugs (M receptor antagonists) exert their effect by blocking cholinergic M receptors, which mediate the contraction of the detrusor, and by inhibiting acetylcholine–M receptor signaling, thereby blocking the involuntary contraction of the detrusor and reducing the overactivity of the bladder. Anti-muscarinic drugs are widely used in the treatment of OAB,^(5,6) but have a number of undesirable side effects. Tolterodine, which is a non-selective and potent M receptor antagonist with similar clinical efficiency but better tolerance, is an alternative choice for treating OAB.^(5,7) Beside medications, OAB can also be treated with implantation of permanent S₃ sacral nerve electrodes coupled to pulse generators for sacral nerve stimulation to electrically stimulate non-muscular afferent sacral somatic nerve fibers, thereby modulating sensory processing and micturition reflex pathways in the spinal cord.^(8,9) As an alternative to the permanent implantation of electrodes, an intermittent percutaneous needle sacral nerve stimulation (IPN-SNS) method has been developed in China, which is a temporary ambulant treatment without surgical intervention and serves the same purpose as the conventional SNS. In this prospective clinical trial, we compared the outcomes of tolterodine only treatment and tolterodine plus IPN-SNS, and hypothesized that IPN-SNS can further enhance the effects of OAB medication.

MATERIALS AND METHODS

Study Patients

The research was approved by the Ethics committee of The Second Hospital of Nanjing, and informed consent was obtained from all par-

ticipants. Female patients from the department of urinary surgery of the hospital who were between 18 and 70 years old and had been diagnosed with OAB, with symptoms persisting for more than 6 months, were included in this prospective trial. The exclusion criteria were as follows: 1) 24-h average urine voided volume more than 200 mL or average urinary frequency less than 8 times; 2) pregnancy, breast-feeding or planned pregnancy; 3) bladder outlet obstruction; 4) abnormal liver or kidney function; 5) urinary infection and 6) contraindication or hypersensitivity to anticholinergic agents. From January 2004 to January 2011, a total of 240 female patients aged 33–65 years old, with an average age of 49.6 years, who met the inclusion and exclusion criteria were chosen for randomization into 2 groups. Before treatment, all patients underwent urinary examinations to exclude urinary tract infection (UTI), urine cytology to exclude urinary carcinoma, urinary ultrasound to determine residual urine, intravenous urography to exclude urolithiasis, as well as cystoscopy and urodynamic examinations to exclude lower urinary tract obstruction and to evaluate detrusor function. None of the patients had a history of stroke, spinal cord injury, or Parkinson's disease. In the tolterodine only group (group 1, n = 120), among 120 patients, 45 had dry idiopathic overactive bladder (IOAB) for an average of 33 ± 16 months and 75 had wet IOAB for an average of 30 ± 16 months. In the IPN-SNS plus tolterodine treatment group (group 2, n = 120), of 120 patients, 47 had dry IOAB for an average of 31 ± 9 months and 73 experienced wet IOAB for an average of 29 ± 12 months. Treatment period in both groups was 3 months (**Figure**).

IPN-SNS Methods

All patients received tolterodine ((LiEnTai®, Sichuan Dikang Sci. & Tech. Pharmaceutical Industry Co., Ltd, Chengdu, Sichuan, China) and IPN-SNS was performed by physicians at the department of urinary surgery. For each treatment session, the patient undergoing surgery was placed in the prone position, with 1 or 2 pillows placed under the lower abdomen and trunk, while the lower limbs were spread at a 30° angle. An insulated needle (Suzhou Medical Instrument Co., LTD, Zhangjiagang City, Jiangsu, China) was introduced percutaneously into the S₃ foramen, located at about 2 cm from the midpoint connection between the superior border line of the sacrum and the coccyx, at a 60° angle with the body surface. A computerized nerve and muscle stimulator (SMY-10A, Shanghai Bang Cheng Industrial Co., LTD, Shanghai, China) was used with a stimulating voltage of 10 V and a pulse frequency of 20–200 Hz, while ensuring that the current intensity could be tolerated by the patients. The duration of each IPN-SNS treatment session was 30 min. The criteria for choosing appropriate currents were as follows: 1) anal contractions; 2) the big toe in the same side bending towards the planter center and 3) the region of the labia having a feeling of tremor. The treatment frequency was once every 2 days in a cycle of 3 months. At the same time, tolterodine (2 mg once daily) was administered, and the control group received only tolterodine (2 mg once daily) for the same period of 3 months. In our hospital, 2 mg is the standard dose of tolterodine, since the recommended dose of 4 mg per day would be too high for the typical body

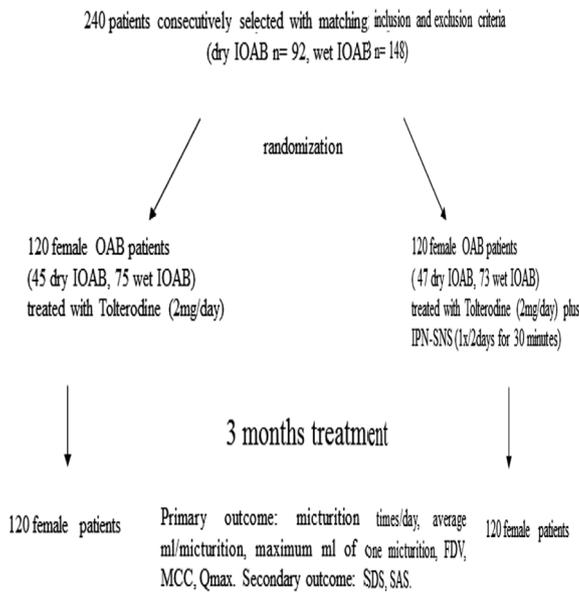


Figure. Study flow chart.

weight of our female patients.

Outcome Measures

The physician in charge noted the medical records, including the patients’ general information, changes in illness state and adverse drug reactions. Data were collected before and at 3 months after the start of the trial. Primary outcome measures were daily average frequency of micturition (times/day), daily average single voided volume (mL/micturition), daily single maximum voided urine volume (mL/micturition), first desire to void (FDV, mL), maximum cystometric capacity (MCC, mL) (Urodynamic Catheter, Laborie Medical Technologies Inc., Ontario, Canada) and maximum flow rate (Qmax, mL/s). Secondary outcome measures were the psychological scores of patients’ self-rating depression scale (SDS) and self-rating anxiety scale (SAS) before and after treatment, which were determined as described elsewhere.⁽¹⁰⁾

Statistical Analysis

Daily average urination frequency, daily average single voided volume, daily single maximum voided volume, FDV, MCC, Qmax and psychological scores of patients’ depression and anxiety before and after treatment were compared, and Prism 5 was used for statistical analysis. Analysis of variance (ANOVA) was utilized for comparing multiple groups and the Bonferroni *t*-test was used for the comparison of 2 groups (groups before and after treatment, control group and treatment group). *P* value < .05 was considered statistically significant.

RESULTS

Patients’ General Characteristics

No obvious differences were observed regarding age, course of disease and urine examination data, including urinary bacterial culture and urinary fungal culture or urine cytology, while urodynamic examinations showed no obstructive diseases in any of the patients. Both the intravenous urography and cystoscopy data were normal, indicating the comparability of the 2 groups (Table 1).

Efficacy of the Combined IPN-SNS and Tolterodine Treatment in Women with IOAB

Results showed that the daily average single voided volume, the daily maximum volume of a single urination, FDV and MCC improved significantly (*P* = .001) with both tolterodine Treatment (Ioccyx) as treatments. The daily average urination frequency and Qmax values also improved in both treatment groups, but without statistical significance. When comparing the outcomes of the 2 different treatments after 3 months, the combination therapy was significantly superior (*P* = .001) for the daily average single voided volume, the daily maximum single volume of urination, as well as for FDV and MCC, compared to treatment by tolterodine only (Table 2).

Efficacy of the Combined IPN-SNS plus Tolterodine Treatment for Improving Depression

We compared self-rating depression scale (SDS) and self-rating anxiety scale (SAS) scores before and after treatment. The normal standard score for SDS is 53; if the score is higher than 53, the patient is likely to be affected by depression. The normal standard score for SAS is

Table 1. Demographic and clinical data of study subjects.

Variables	Group 1 (n = 120)	Group 2 (n = 120)	P Value
Age, years	52 ± 11	54 ± 13	> .05
Duration of symptoms (months)	33 ± 16	30 ± 11	> .05
Urine test data			
Bacterial culture	Negative	Negative	1.0
Fungal culture	Negative	Negative	1.0
Cytology	Negative	Negative	1.0
Residual urine, mL	0.0	0.0	1.0
Urodynamic study	No obstructive disease	No obstructive disease	1.0
Intravenous urography	Normal	Normal	1.0
Cystoscopy	Normal	Normal	1.0

Table 2. Outcome measures in both study groups.

Variables		IPN-SNS Plus Tolterodine		Tolterodine Only	
		Dry IOAB (n = 47)	Wet IOAB (n = 73)	Dry IOAB (n = 45)	Wet IOAB (n = 75)
Urinary frequency (times/day)	Before Treatment	23 ± 10	22 ± 11	23 ± 11	23 ± 10
	After Treatment	10 ± 7	10 ± 7.5	20 ± 12	18 ± 11
	Effect size	-1.30	-1.09	0.27	-0.5
Single voided urine volume (mL/times)	Before Treatment	119 ± 71	126 ± 84.5	117 ± 75	121.5 ± 74.5
	After Treatment	245 ± 47*	245.5 ± 69*	150 ± 77*♦	157 ± 63.5♦
	Effect size	1.77	1.47	0.44	0.48
Maximum single voided urine volume (mL/times)	Before Treatment	154 ± 34	146 ± 43.5	161 ± 86	148.5 ± 60.5
	After Treatment	315 ± 77*	323 ± 61.5*	212 ± 44*♦	206 ± 61*♦
	Effect size	4.73	4.07	0.59	0.95
First desire to void (mL)	Before Treatment	116 ± 47	113 ± 57.5	108 ± 50	110 ± 52.5
	After Treatment	176 ± 64*	187 ± 63*	142 ± 44*♦	140 ± 52*♦
	Effect size	1.28	1.29	0.68	0.57
Maximum cystometric capacity (mL)	Before Treatment	166 ± 69	157 ± 61.5	164 ± 60	160 ± 52
	After Treatment	265 ± 46*	287.5 ± 45*	203 ± 50*♦	193 ± 42.5*♦
	Effect size	1.43	2.11	0.65	0.63
Maximum flow rate (mL/s)	Before Treatment	12.8 ± 5.1	12.2 ± 4.3	12.9 ± 4.8	11.9 ± 3.9
	After Treatment	20.1 ± 3.3	21.2 ± 3	18.1 ± 2.9	18 ± 3.2
	Effect size	1.41	2.09	1.08	1.56

Abbreviations: IPN-SNS, intermittent percutaneous needle sacral nerve stimulation; IOAB, idiopathic overactive bladder.

**P* < .001 when compared with pre-treatment.

♦ *P* < .001 when compared with IPN-SNS plus tolterodine.

50; if the score is higher than 50, the patient is likely to be affected by anxiety. The results showed that the SDS and SAS scores were significantly lower (*P* < .001) after treatment than before in both groups, but the combined treatment led to statistically significantly better outcomes (*P* < .001) than the medication only treatment (Table 3). Taken together, these results indicate that the combined treatment with IPN-SNS plus tolterodine has improved patients' quality of life to a sig-

nificantly greater extent than tolterodine alone (Table 3). No obvious recurrence was noticed after 12 months of follow-up among patients in group 2.

DISCUSSION

Our hospital has been carrying out IPN-SNS and tolterodine treatments since 2004. Among the 240 female patients admitted to our hospital, urinary frequency, average voided volume, and single maximum void-

Table 3. Efficacy comparison of tolterodine plus IPN-SNS and tolterodine only treatments for improving depression.

Psychological Measures		IPN-SNS Plus Tolterodine		Tolterodine Only	
		Dry IOAB (n = 47)	Wet IOAB (n = 73)	Dry IOAB (n = 45)	Wet IOAB (n = 75)
Self-rating depression scale	Before Treatment	61 ± 5.2	60 ± 5.1	61 ± 5.5	59.8 ± 5.8
	After Treatment	33 ± 6.2*	32.3 ± 6.6*	44.0 ± 5.9*♦	43.1 ± 5.6*♦
	Effect size	-5.38	-5.43	-3.09	-2.88
Self-rating anxiety scale	Before Treatment	60.6 ± 7.7	59.6 ± 7.9	60.4 ± 7.0	61 ± 7.5
	After Treatment	30.3 ± 4.4*	32.6 ± 5.3*	41.3 ± 4.4*♦	43 ± 6*♦
	Effect size	-3.93	-3.42	-2.73	-2.40
Maximum flow rate (mL/s)	Before Treatment	12.8 ± 5.1	12.2 ± 4.3	12.9 ± 4.8	11.9 ± 3.9
	After Treatment	20.1 ± 3.3	21.2 ± 3	18.1 ± 2.9	18 ± 3.2
	Effect size	1.41	2.09	1.08	1.56

Abbreviations: IPN-SNS, intermittent percutaneous needle sacral nerve stimulation; IOAB, idiopathic overactive bladder.

**P* < .001 when compared with pre-treatment.

♦ *P* < .001 when compared with IPN-SNS plus tolterodine.

ed volume in the 2 groups treated with tolterodine improved statistically significantly, but these outcomes were statistically significantly superior for patients treated with IPN-SNS plus tolterodine. SNS involves an interventional technique, which continually delivers short electric pulses to stimulate specific sacral nerves (S_3 or S_4) in order to disrupt psychologically misleading electric signals generated by nerve cells. The external stimulation serves to artificially activate excitatory and inhibitory neural pathways, to disturb an abnormal sacral nerve reflex arc, and to affect and mediate the behavior of effector organs dominated by the sacral nerves of the bladder, urethral sphincter, and pelvic floor, thus providing neuromodulation.⁽⁸⁾ It has been reported that urinary frequency and urgency syndrome, as well as urgent incontinence, are often associated with detrusor overactivity, which can be inhibited by stimulating the ano-rectal branch of the pelvic floor nerve, pudendal nerve and lower limb nerves. In addition, the spinal cord inhibitory pathway can also be activated through stimulating S_3 afferent nerves.⁽¹¹⁾ Stimulation of the pelvic floor sensory afferent nerve pathway can restrain impulses of the detrusor motor neurons at the spinal cord level, so that micturition reflexes or unstable contractions of the detrusor are inhibited.⁽¹²⁻¹⁴⁾ SNS treatment of OAB is considered to be safe, as well as feasible and with the improved technology of therapy devices, SNS is increasingly applied for the treatment of OAB.^(9,15,16) Moreover, SNS is a bridge connecting a conservative treatment with radical invasive techniques and has already become a widely accepted treatment for OAB.⁽¹⁷⁾ Up to now, there have been few reports describing the combined use of SNS and OAB medications. The common application of SNS is the surgical implantation of a permanent electrode in one of the sacral foramen, which is connected to a subcutaneously placed pulse generator via an extension lead. In our clinical experience, many patients, particularly those who are middle-aged, cannot accept this procedure. As an alternative, we developed the IPN-SNS treatment, in which the electrical stimulation is periodically applied in the hospital without surgical intervention. The disadvantage of this approach is the relative long period without electrical stimulation between treatments. At present, tolterodine is the number one choice for the medical treatment of OAB, but there is room for improvement.⁽¹⁸⁾ In our study, we found that the addition of IPN-SNS to tolterodine could substantially improve treatment outcomes, leading to significantly reduced SDS and SAS scores after 3 months of combination therapy. A limitation of our study is the relatively small number of patients used; therefore, the results need further validation by larger trials. In addition, the IPN-SNS treatment is laborious and requires a lot of work by clinical staff, particularly for large patient groups. Furthermore, the results cannot be generalized to all patient groups, especially in view of the reduced tolterodine dosage used in our specific settings.

CONCLUSION

In summary, our study has demonstrated that it is safe and feasible to adopt a combination treatment of IPN-SNS plus tolterodine for OAB,

and that such combined treatment can lead to improved outcomes when compared to treatment by tolterodine only.

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CONFLICT OF INTEREST

None declared.

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