World Journal of Urology (2019) 37:2481–2492
https://doi.org/10.1007/s00345-019-02698-7

ORIGINAL ARTICLE

Remotely programmed sacral neuromodulation for the treatment of patients with refractory overactive bladder: a prospective randomized controlled trial evaluating the safety and efficacy of a novel sacral neuromodulation device

Yaoguang Zhang[1,9] · Peng Zhang[2] · Xiaojun Tian[3] · Guoqing Chen[4] · Yan Li[5] · Yong Zhang[6] · Zhihui Xu[7] · Zhongqing Wei[8] · Wei Zhang[1,9] · Lulin Ma[3] · Benkang Shi[5] · Limin Liao[4] · Jianye Wang[1,9]

Received: 5 December 2018 / Accepted: 19 February 2019 / Published online: 26 February 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Purpose The efficacy and safety of a novel remotely programmed BetterStim sacral neuromodulation (SNM) system was evaluated in patients with refractory overactive bladder (OAB) in a prospective, controlled, multicenter trial.

Methods A total of 84 patients referred for SNM therapy from October 2015 to January 2018 were studied. Of the patients who qualified for implantation, 37 and 33 were randomly assigned to treatment and control groups, respectively. Patients in the treatment group underwent stimulation upon implantation, while stimulation was delayed in the control group for 3 months. Follow-up visits, consisting of voiding diary outcome, questionnaires regarding overactive bladder symptom score (OABSS) and quality of life were conducted at 1, 3, and 6-month post-implantation.

Results Compared with the control group, subjects in the treatment group exhibited statistically significant improvement in OAB symptoms at 3 months. The overall success rate was achieved in 72% of the treatment group, compared with 12% of the control group at 3 months. At 6 months, there were no significant differences in key voiding diary variables between the two groups. Further, this study demonstrated sustained improvement in urinary symptom interference in OAB patients. In addition, nearly all patients expressed great satisfaction with the remote-programming methods. No serious adverse events occurred, and device-related adverse events rate was 12.86%.

Conclusion This clinical study demonstrates subjective and objective success of the BetterStim SNM system. Importantly, our data suggest that remote programming can be safely used as a viable option for the conventional programming with a high degree of patient satisfaction.

Keywords Electric stimulation · Urinary bladder · Randomized controlled trial · Overactive bladder · Programming

Introduction

Overactive bladder is a common and chronic clinical syndrome, defined as urinary urgency with or without frequency, typically accompanied with incontinence and nocturia, which becoming a growing problem worldwide [1]. The prevalence is estimated at approximately 16.9% in the adult population and increases with age in the United States [2–4]. The total prevalence of OAB is approximately 6.0% in China [5]. Despite the considerable limitation of social activities and impact of OAB on quality of life, patients rarely seek therapeutic options. For management of refractory overactive bladder, the widely applied sacral neuromodulation therapy may serve as a promising treatment option, with compelling efficacy for OAB symptoms [6–10]. Over the past decades, SNM therapy has gained global acceptance in urological practice and > 250,000 patients have been treated worldwide.

The technique has evolved since its inception by Schmidt et al., with the use of tined lead, as well as the development

Yaoguang Zhang and Peng Zhang contributed equally to this work.

✉ Limin Liao
lmliao@263.net

✉ Jianye Wang
jianye_wangbhp@126.com

Extended author information available on the last page of the article

of rechargeable SNM system [11, 12]. However, the SNM system available and approved for use in voiding dysfunctions remains as non-remote programming [6, 13]. Patients require frequently follow-up postoperative programming, and need to come back to hospitals for ensuring the implanted devices are working at optimal programmable parameters and troubleshooting of the implanted devices in vivo. With the popularity of telemedicine, remote point-to-care programming of neuromodulation devices would benefit more patients who live far away from local hospitals.

Currently, a novel BetterStim SNM system (PINS, Beijing, China), manufactured by Beijing PINS Medical Co., Ltd., in cooperation with the National Engineering Laboratory for Neuromodulation, Tsinghua University, is designed to provide a miniaturized, real-time remote-programming system, adjusting the programming parameters timely as tissue impendence changes over time, resulting in continuous and stable clinical benefits. The BetterStim SNM (PINS, Beijing, China) device utilized in the present study includes two series of implantable pulse generator (IPGs): G131 and G132, while the basic components are similar with other SNM systems [6, 12]. The BetterStim IPGs utilize titanium construction and have a volume of 25 cc (dimensions: $47 \times 51 \times 10.5$ mm^3, weight: 35 g) for G131 model and 15 cc (dimensions: $50 \times 50 \times 6.8$ mm^3, weight: 25 g) for G132 model, which is comparative with the 14 cc Medtronic InterStim II. And the battery capacity of G131 and G132 is 2500 mAh and 1850 mAh, respectively, while the InterStim II has a capacity of 1300 mAh, equating to a 30% smaller battery life. Additionally, the BetterStim system could be current controlled or voltage driven, and delivers constant current or voltage stimulation for SNM therapy. As for the BetterStim tined lead, four similarly sized and spaced electrodes to the InterStim lead, measure with three lengths 28, 33 and 41 for different sized patients. One of the most notable differences of the BetterStim system is the significant function of remote controlling, which was refined and well described previously [14]. The remote-programming system is a secure and robust Internet-based system, involving in the application of a virtual network combined with point-to-point encryption software that met recognized standards. Figure 1 shows the general architecture of the real-time remote-programming system: Physician Client, Patient Client, Server Station and Video Communication System. The Physician Client was designed to be located at a personal computer (PC) as the terminal hardware, with strong operability and mobility. Physician could visit the Server Station through a web browser and get detailed information of their patients as well as stimulators. Patient Client was designed as a home terminal for adjusting parameters and uploading follow-up history records. The entire

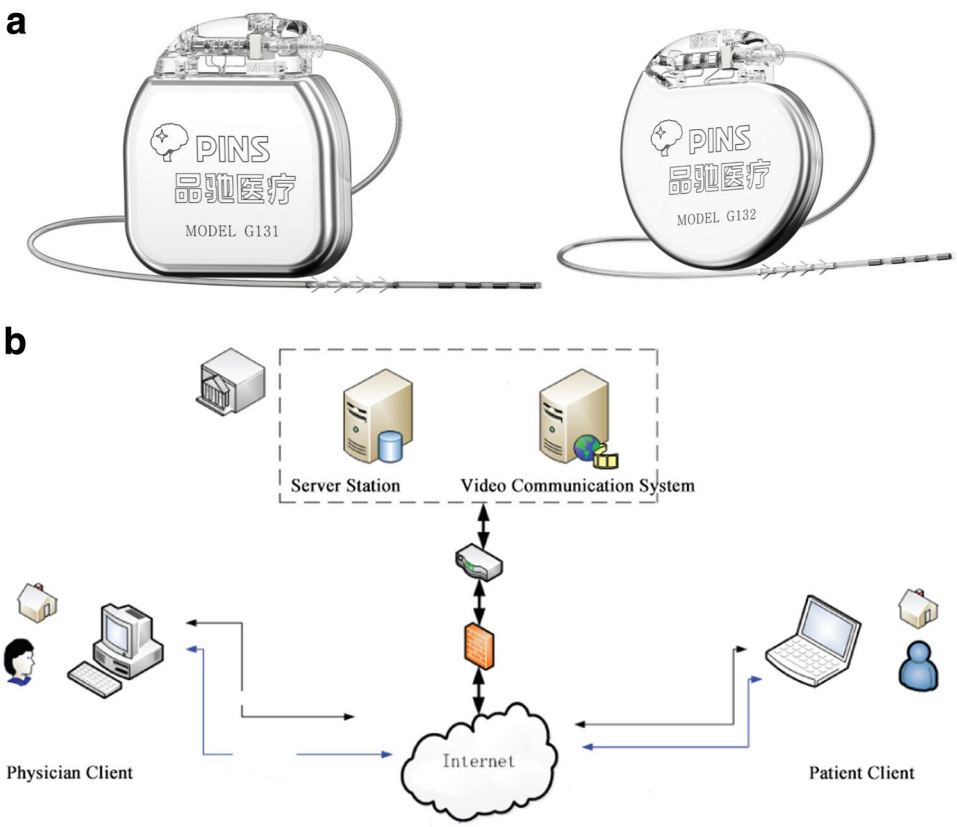

Fig. 1 The remote sacral neuromodulation (SNM) implantable pulse generator system. **a** The SNM implantable pulse generator. **b** Schematic diagram of the wireless and remote-programming system, including the physician client, patient client, server station and video communication system

Patient Client hardware consists of four parts: PC, Bluetooth dongle, programmer and in vivo IPG. The PC is a commercial telephone equipped with a special patient client software downloaded from App store, applying for connecting with the physicians and received programming parameters. The Bluetooth dongle is a custom-built hardware interface and connects to the PC via a USB interface. The programmer installed with a Bluetooth salve unit to exchange data with the Bluetooth dongle and control the in vivo stimulators. The Server Station is established duplex communication channels in which session messages and adjustment parameters are transmitted to the clients and data are stored on the database server. The Video Communication System consists of a live face-to-face electronic audiovisual interaction between the provider and patients. Video was captured by Portable digital USB cameras and microphones. Video (FLV format) and audio (SPEEX format) would be automatically attached into the media stream. The Physician and Patient Client were virtually linked by the Server Station. Via this communication link, the instruction of parameter adjustment was stored and sent to the Patient Client, then transmitted through a wireless link to a patient programmer. Once the implanted stimulator received the instruction from patient programmer and finished the execution, the Patient Client uploaded results and follow-up history records to the Sever Station. SSL protocol and certificate identity authentication were used to establish communication link between the Patient Client and the Server station. The entire remote-programming progress was accompanied by synchronistical visual communication provided by the Video Communication System.

Compared with conventional programming methods, the BetterStim system has significant advantages within all stages of programming, which would reduce costs and travel time for patients, improving patient satisfaction, and facilitate quality care for complex patients [15]. Further, the platform provides real-time remote control service which allows clinicians to directly check the parameters' history records. Some practices such as Bomin Sun use point-to-care programming technology in lieu of conventional programming to see the postoperative Deep Brain Stimulation (DBS) patients, which showed no significant difference in the accuracy of clinical outcomes of programming between the conventional and remote-programming sessions [16, 17]. Additionally, programming parameters of the BetterStim system including amplitude (0–10 V or 0–25 mA), pulse width (30–450 μs), and frequency (2–40 Hz) can be adjusted either by conventional programming or by remote-programming method. To ensure the security of the data transmission, the Physician Client was equipped with a client certificate as an identity authentication which would be examined by the Server Station before the browser gets data. Thus, remote programming can safely use as well as routine postoperative clinic visits in programming.

To confirm the efficacy and safety of this novel remote-programming SNM device (PINS, Beijing, China), we conducted a prospective, multi-center, randomized, control clinical trial in China. The study consisted of an effective analysis that compared OAB clinical therapeutic success in a subset of patients randomized to SNM stimulation ON group or SNM stimulation OFF group and were then followed for 6 months. The primary hypothesis of this randomized procedure was that SNM stimulation would significantly improve OAB symptoms of patients by at least 30% of success rate, superior to SNM OFF group.

Materials and methods

Study design and population

A multi-center, randomized, controlled follow-up study was conducted at eight centers in China and approved by the ethical committees of each center. The patients were recruited from the general urological population between October 2015 and January 2018, and each patient signed an informed consent form prior to study participation. The study was designed using the recommendations of the Consolidated Standards of Reporting Trials (CONSRT) statement [18]. Figure 2 shows an overview of the procedures in this study.

All participants had a primary diagnosis of OAB and/or OAB symptoms, as demonstrated on a 5-day voiding diary, and had experienced previous treatments failure with at least one anticholinergic medication or could not tolerate more conservative treatments (e.g., pelvic floor, biofeedback, oral pharmacotherapy) [6, 12]. Treatment failure was defined as having a treatment discontinuation (treatment gap of $\geq$ 45 days) or switching anticholinergic therapy [19]. The definition of refractory to standard medical therapy was considered that subjects failed or could not tolerate at least one anticholinergic medication and have at least one anticholinergic medication not yet attempted. The details of the inclusion and exclusion criteria are provided in Table 1.

Study procedures

Based on the initial results, consisting of medical history, urodynamic testing, and baseline voiding diary information, a total of 84 OAB cases, meeting all inclusion criteria, were enrolled in the study. Participants underwent a two-stage implant procedure with the IPG implantation system requiring a 14-day test stimulation period. The first stage refers to the implanting of a permanent lead for testing the response to SNM under general anesthesia. Standardized electrode placement technique was described in great detail and used

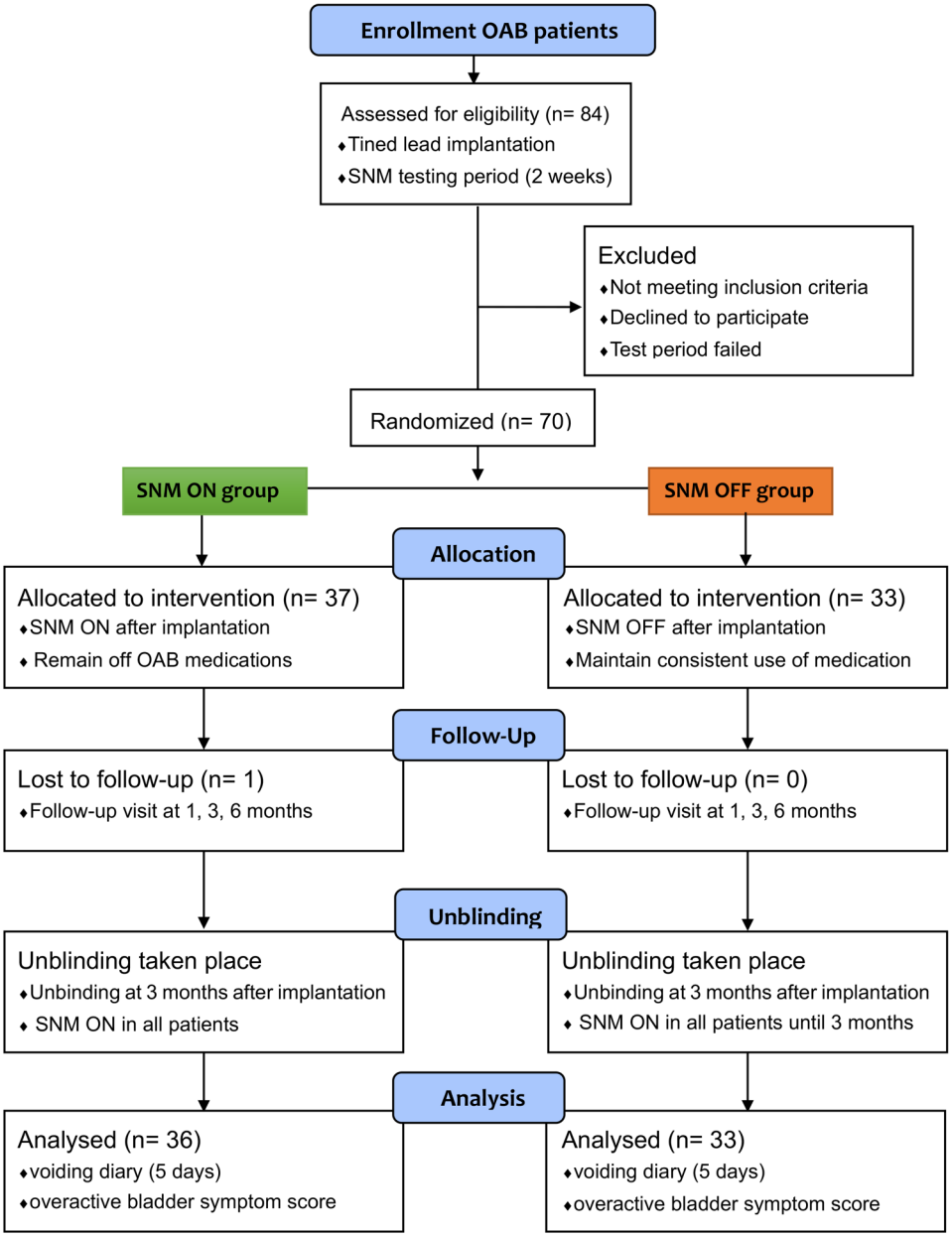

Fig. 2 Flowchart of the sacral neuromodulation clinical trial

the same procedure previously described for InterStim system [20]. Fluoroscopic guidance was used to implant the tined lead along the S3 sacra nerve root. It was recommended to give one dose of intravenous prophylactic antibiotics before SNM system implantation. In general, broad spectrum oral antibiotics were recommended for a period of 5–7 days after operation. Test stimulation success was considered as a $\geq 50\%$ improvement from baseline in key voiding variables [either in average voids/day or a return to normal voiding (< 8 voids/day) or average leaks/day] based on voiding diaries. After completion of test stimulation, those who met success criteria were implanted permanently with the neuromodulator. A pocket was made in the upper buttocks area to accommodate the IPG, and the tined lead was tunneled subcutaneously to the neurostimulator pocket. The neurostimulator and lead were connected and placed in the pocket. Then patients were randomized to treatment (stimulation ON) group or control (stimulation OFF) groups at a 1:1 ratio. An independent investigator performed the randomization and an online random number generator was applied to generate the random sequence (https://www.random.org/). All participants were unaware of the allocation.

After randomization, the stimulator was turned ON for each patient in the treatment group and the effectiveness of neuromodulation, as determined by the stimulation parameters, was optimized by an investigator not involved in

Table 1 List of selection criteria for patients with overactive bladder (OAB)

Inclusion criteria
Age greater than 16 years
Diagnosis of OAB as demonstrated on a 5-day voiding diary defined as ≥ 8 voids/day, and/or a minimum of 2 involuntary leaking episodes in a 72 h period
Refractory to standard medical therapy
≥100 mL bladder capacity with normal upper urinary tract
Good surgical candidate
Able to complete study documentation and return for follow-up evaluation
Exclusion criteria
Neurological conditions that may interfere with normal bladder function, including multiple sclerosis, spinal cord injury, or stoke occurs in the past 3 months
Primary stress urinary incontinence
Current symptomatic urinary tract infection (UTI)

evaluation of the clinical outcome. In the control group, the stimulator was turned OFF and patients followed their doctor's advice for medical therapy and maintained consistent use of any OAB medication (anticholinergic, antimuscarinic or tricyclic antidepressant) until 3 months. At the 3-month visit, unblinding was performed and the neuromodulator was turned ON in all patients.

Follow-up visits

All participants returned for follow-up visits post-implant at various time points, including 1, 3, and 6-month visits to assess initial response to therapy. A voiding diary, OABSS questionnaire, and medical history were collected to assess the response to treatment in each follow-up visit. Unscheduled follow-up visits were allowed as needed to adjust stimulation parameters to optimize therapy, either performed by conventional or remote programming. If both the patient and the physician felt remote programming was acceptable in lieu of an actual clinic visit, the patient's scheduled clinic appointment would be canceled. During follow-up visits, all adverse events (AEs), defined as device-related AEs, medication-related AEs or remote-programming related AEs, were documented.

Outcome measures

The primary outcome was the clinical therapeutic success rate of SNM, determined by voiding diary collected at the 3-month follow-up visit. The success rate was designated as participants with OAB symptoms had to demonstrate $a \geq 50\%$ improvement in average voids/day or average leaks/day compared with baseline values or a return to normal voiding frequency (< 8 voids/day). A participant was counted if she/he met the definition of clinical therapeutic success.

Secondary outcomes were the changes from baseline in mean number of leaks/day, voided volume/void, urinary urgency episodes per day, or voids/day over the first 6 months after implantation (1, 3, and 6-month assessments), based on the use of monthly 5-day voiding diary at each of those time points. Further, secondary outcomes including changes from baseline in the health-related quality of life and OABSS at the 3-month, and 6-month post-implant visits. Additionally, patient satisfaction and adverse events were evaluated.

To assess OAB-related quality of life (OABqol), changes through 6 months were calculated by comparing baseline values from follow-up visits. An interference question on the OABqol, "Overall, how much do your urinary symptoms interfere with your everyday life?", was measured on a scale, from 0 to 10 [21]. In addition, patient's satisfaction was evaluated by satisfaction questionnaire.

Sample size

The sample size was calculated using PASS version 12.1 software and determined by the clinical therapeutic success rate at the 3-month follow-up visit. We assumed that the success rate at the 3-month visit would be 30% in the control group and 60% in the treatment group. Success rates were estimated from previous studies with 76% for SNM and 49% for standard medical therapy [6]. The sample sizes were designated to provide 80% power for a one-tailed test, alpha = 0.025, comparison of 3-month OAB therapeutic success rates, with a 10% loss-to-follow-up rate. These calculations revealed that 68 individuals (34 per group) must be included.

Statistical analysis

Demographic and clinical data were collected at the time of presentation and analyzed using SAS version 9.4 software (version number: 11202165). All statistical tests were two-sided and a value of $P < 0.05$ was considered statistically significant. The continuous variables would be summarized with means and standard deviations (SD). A *t* test was used to assess comparisons between groups, and the Chi squared test or Fisher's exact test was applied for comparison of categorical variables.

Results

Demographic characteristics

Overall, 84 patients with OAB completed test stimulation and 70 patients received a full system implant, resulting

in an overall implant rate of 83%. All 70 patients with full system implants were randomized, 37 were allocated to the treatment group and 33 to the control group. Study outcome data remained blinded until the 3-month follow-up visit of the randomized participants was completed. 69 patients reached the 6-month post-implant visit, of whom 74% were females and 26% were males. Baseline demographics are presented in Table 2. There were no significant differences between the two groups in terms of demographics, baseline assessments, or medical history. Mean age with standard deviation (SD) at test stimulation was 54.31 ± 15.41 years (range 21.95–76.30). All patients were treated with long-term conservative therapy with a mean preadmission treatment period of 6.53 ± 5.30 years, which yielded poor efficacy or intolerance. Of the 70 patients, 60 (86%) had received pharmacological treatment, 30 (46%) had undergone surgical interventions, including intravesical endotoxin injection before the study.

Implant outcome

Efficacy at 3 months: results at the 3-month visit were available in 36 and 33 patients in the treatment and control groups, respectively. One patient in the treatment group was lost to follow-up. According to the statistical analysis, the average number of voids per day at baseline for patients was 28.27 ± 12.52, which decreased to 14.99 ± 7.98 at 3-month follow-up in the treatment group (Fig. 3a, $P < 0.001$). Compared to the control group, the treatment group significantly reduced the urinary urgency episodes (Fig. 3b, $P < 0.01$). Additionally, the voided volume per void increased post-implantation (Fig. 3c, $P < 0.05$), as well as the OABSS was visibly reduced than the control group (Fig. 4c, $P < 0.05$). Symptoms of urge incontinence at 3 months were significantly reduced in the treatment group (Fig. 3d, $P < 0.05$). In contrast, the control group patients showed no significant improvement in OAB symptoms at 3 months (Figs. 3, 4c). Changes from baseline in OAB symptoms between the two groups revealed great improvement in the treatment group, compared with the control group. As shown in Fig. 4, the analysis suggested an OAB therapeutic success rate of 72% in the treatment group, compared with 12% in the control group ($P < 0.001$).

Efficacy at 6 months: Voiding diaries were available for 69 patients at 6 months. As documented in the voiding diary analysis results, 33 patients in the control group exhibited a significant reduction in the average number of voids per day and the urinary urgency episodes per day, compared with baseline (Fig. 3a, b, $P < 0.05$). For the urinary incontinence patients, 9 patients in the control group and 11 patients in the treatment group showed great improvement in leaks. Over 6 months, both groups improved on the urinary symptoms, with the overall OAB therapeutic success rate was 69% and 61% in the treatment and control group, respectively. Further, there was no significant difference in the key voiding symptoms between the two groups. Therapeutic success rates and voiding variables suggest that the effectiveness of SNM therapy was sustained through 6-month post-implantation (Fig. 4a).

Changes from baseline in OABqol between the two groups suggested greater improvement in the treatment group, compared with control group, at the 3-month follow-up visit. A total of 78% of subjects in the treatment group reported an improved or greatly improved urinary symptom

Table 2 Baseline demographics and medical history

Demographic	Control group ($N = 33$)	Treatment group ($N = 37$)	P value
Gender			
Female	24 (72.73%)	27 (72.97%)	0.982
Male	9 (27.27%)	10 (27.03%)	
Age, years	50.36 ± 16.33	54.67 ± 15.16	0.254
Number of previous medications	1.69 ± 1.49	1.75 ± 1.32	0.728
Baseline voids/day	30.14 ± 17.30	28.27 ± 12.52	0.874
Baseline urgency of voids	2.77 ± 1.40	3.16 ± 1.33	0.244
Baseline void volume/void (mL)	87.19 ± 54.98	101.41 ± 53.41	0.219
Baseline leaks/day	1.42 ± 3.89	2.47 ± 5.94	0.281
OABSS domains			
Frequency	1.76 ± 0.50	1.86 ± 0.35	0.373
Nocturia	2.91 ± 0.29	2.78 ± 0.58	0.362
Urinary urgency	4.55 ± 0.90	4.32 ± 1.08	0.228
Urgency urinary incontinence	0.85 ± 1.72	1.19 ± 1.84	0.364
Total	10.06 ± 2.14	10.16 ± 2.18	0.711

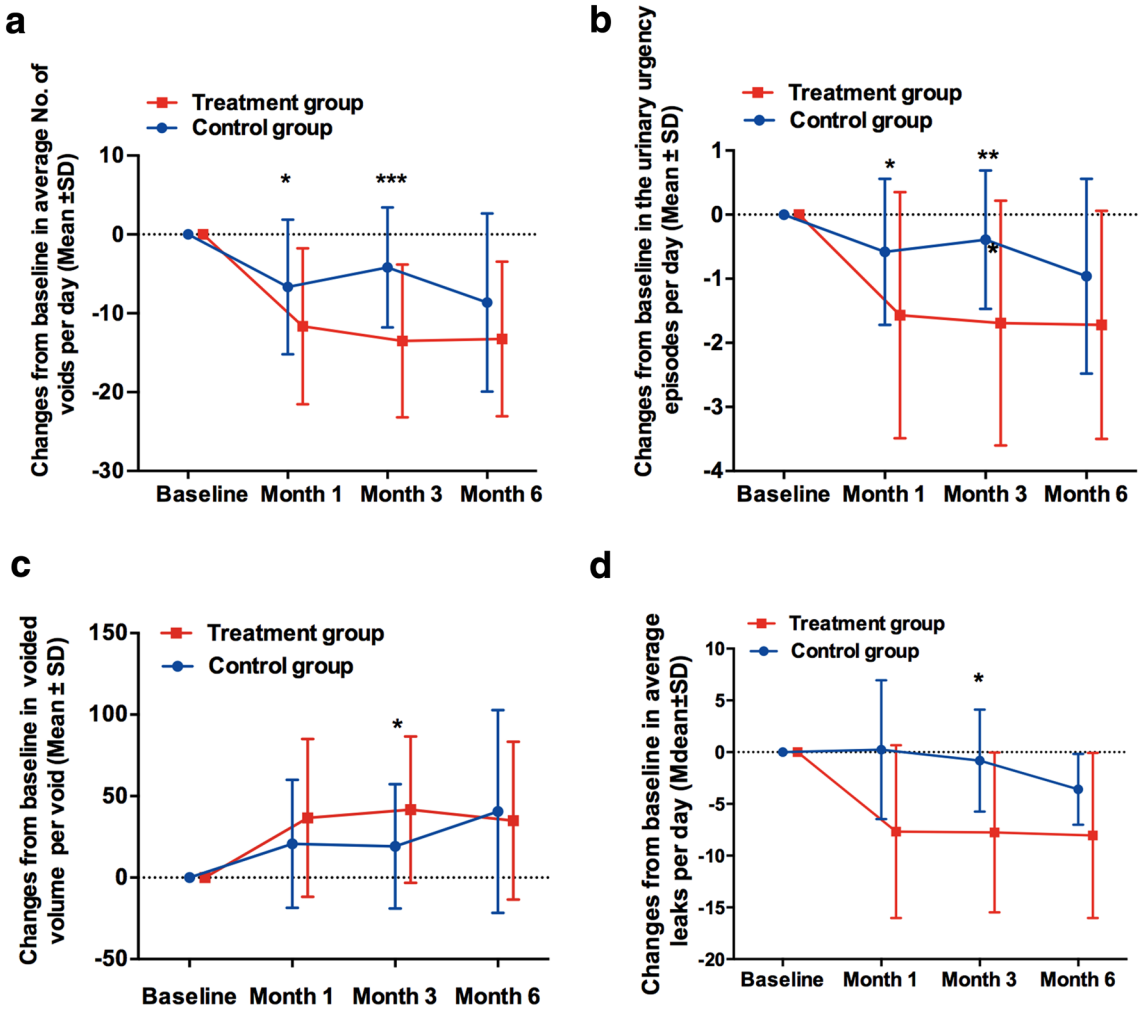

Fig. 3 Voiding symptoms in overactive bladder (OAB) symptoms between the treatment and control groups over time. **a** Changes from baseline in the average number of voids per day ($n=69$ all subjects, $n=33$ control group, $n=36$ treatment group). **b** Changes from baseline in the urinary urgency episodes per day ($n=69$ all subjects, $n=33$ control group, $n=36$ treatment group). **c** Changes from baseline in voided volume per void ($n=69$ all subjects, $n=33$ control group, $n=36$ treatment group). **d** Changes from baseline in the leaks per day ($n=20$ urinary incontinence subjects, $n=9$ control group, $n=11$ treatment group). $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ for significant difference between the treatment and control groups

interference score at 3 months, as compared to 6% in the control group (Fig. 4b, $P<0.001$). At the 6-month follow-up visit, all participants in each of the two groups showed greater improvement of urinary symptom interference score, and there was no significant difference between two groups (Fig. 4b, d).

Adverse events

Implant safety was evaluated through adverse event reports. During the 6-month follow-up visit, there were no unanticipated serious device-related AEs. Thirty-two events (25.71% of subjects) reported throughout the study period up to the 6-month visit. Specifically, device-related AEs occurred in 12.86% (9/70) of participants during the full system implant, comprising of implant site pain (2.86%, 2/70), undesirable change in stimulation (2.86%, 2/70), and loss of efficacy (7.14%, 5/70), resolved through device reprogramming. There were no serious AEs reported related to the implantable device. Further, no adverse events occurred related to remote programming.

Remote programming

According to our questionnaire results, postoperative follow-up burden was quantitatively evaluated by the average interval of clinical visits, travel distances, and general cost of a single follow-up. The mean travel distance from home to hospital is 1364.98 ± 764.93 km. 53% participants spend 500 RMB for each follow-up visit while 48% participants visit

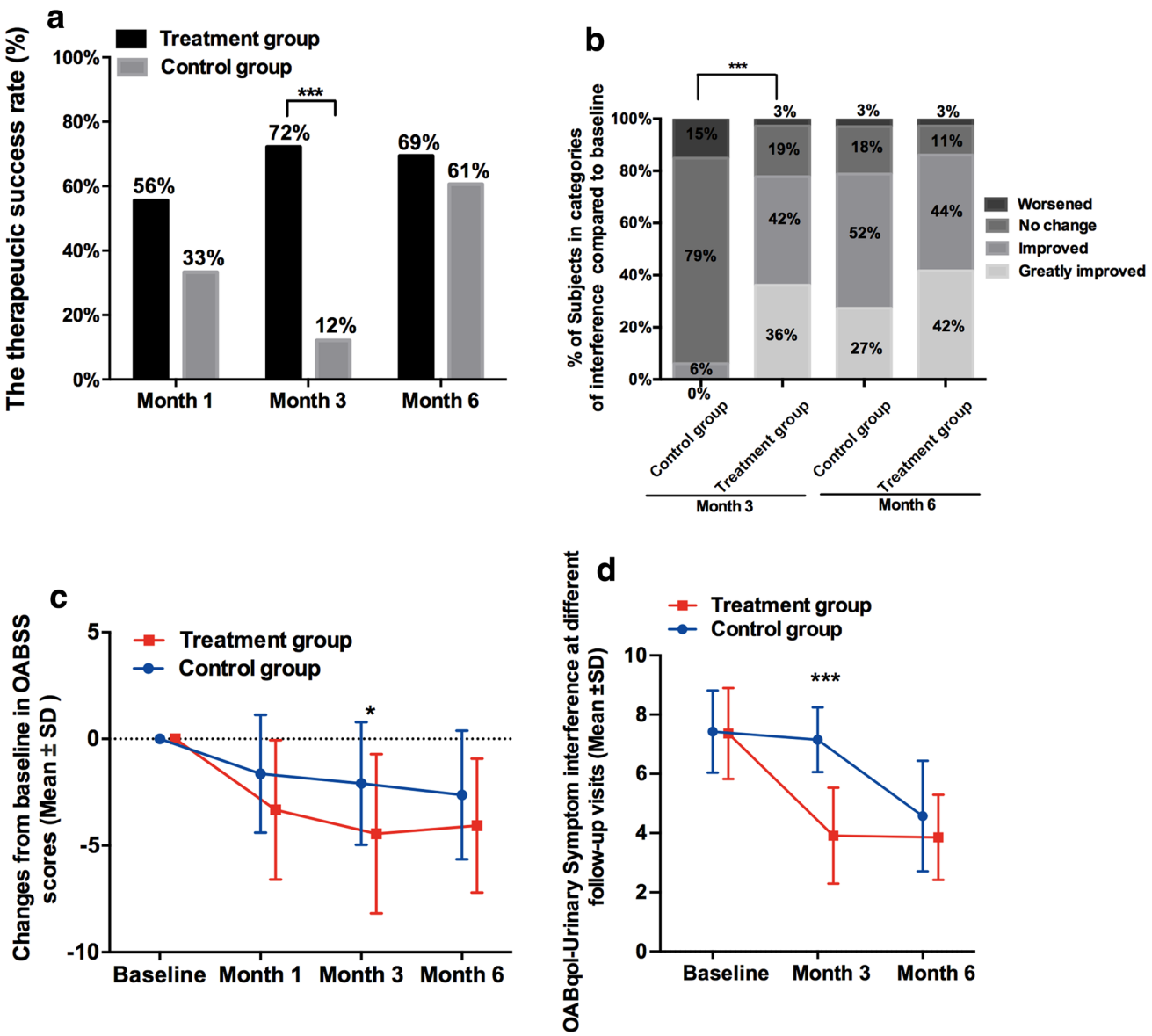

Fig. 4 Comparison of overall overactive bladder (OAB) therapeutic success rate and the overactive bladder quality of life (OABqol)-urinary symptom interference between the control and treatment groups. **a** OAB therapeutic success rate was defined as the percentage of patients that obtained $a \geq 50\%$ improvement in either of the key voiding diary variables, compared with baseline. **b** The difference between patient groups in the improvement of urinary symptom interference from baseline. **c** Changes from baseline in the OAB symptom score (OABSS). **d** OABqol-urinary symptom interference at different follow-up visits in OAB patients between the two groups. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ for significant difference between the treatment and control groups

hospital more than 4 times per month (Fig. 5a, b). Whereas patients selected remote programming, only need to stay at home with network coverage, regardless of distance.

During the follow-up visits, nearly 57 subjects received remote controlling, as well as conventional programming was performed in 70 patients to achieve maximal therapeutic benefit. Performance and parameter settings between this two programming methods were statistically indistinguishable (Fig. 5c, d). Complications related to remote-programming occurred in any session were zero. None of the patients experienced signal corruption during programming. With exception of a slightly delay of video signal existed in remote-programming session, there was no substantial difference in time commitment with programming conducted remotely or in-person. Indeed, time consume of the remote programming was more focused, with less tangential discussion. The mean frequency of setting up communication between patients and physicians was 1.68 ± 1.01 times. Interruptions occurred in remote programming were regarding to the limited speed Internet connectivity and improper operation, which could be

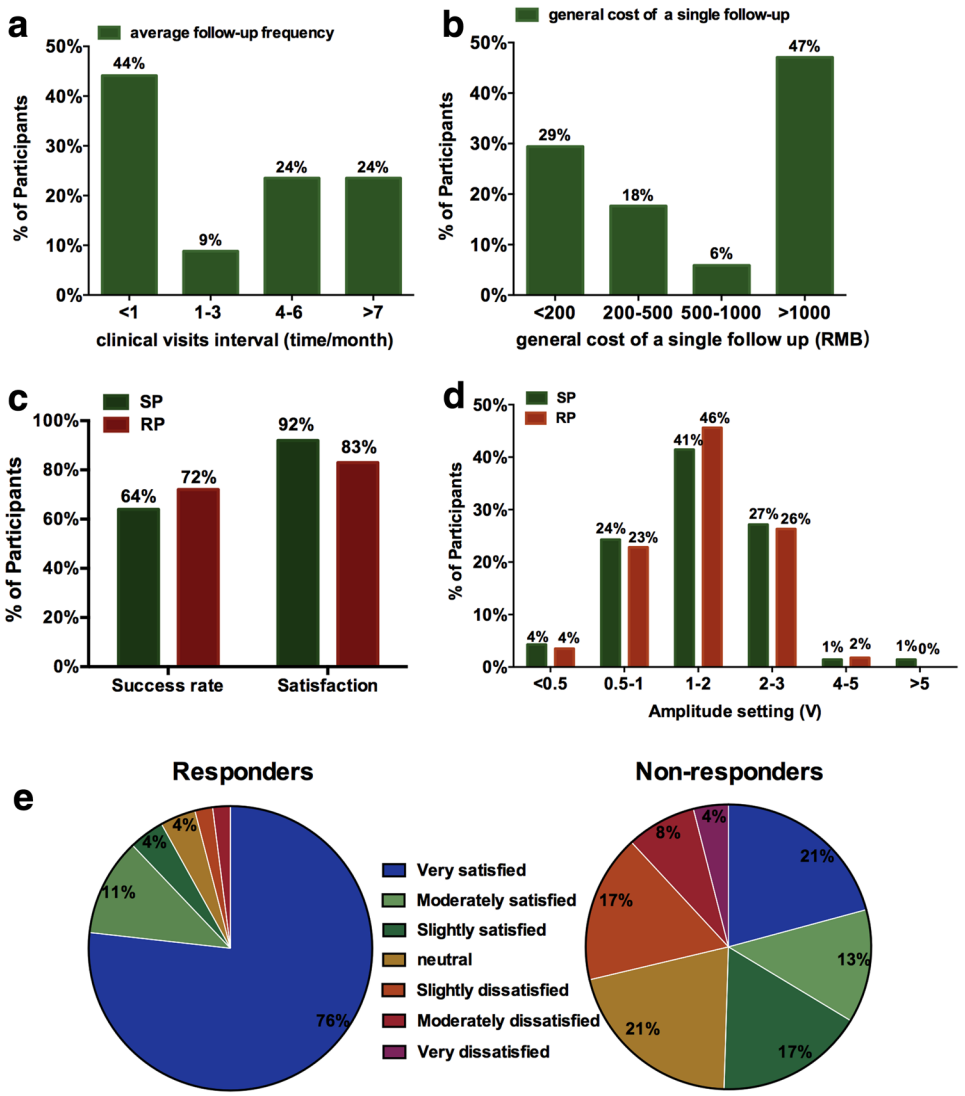

Fig. 5 Patient satisfaction with the remote-programming sacral neuromodulation (SNM) system. **a** The average total cost for each follow-up (RMB). **b** Patient's average interval of clinical visits per month. **c** The therapeutic success rate and satisfaction in patients referred to standard programming and remote-programming methods. *SP* standard programming, *RP* remote programming. **d** Amplitude settings in overactive bladder patients with different programming methods. *SP* standard programming, *RP* remote programming. **e** Patient satisfaction with the remote-programming sacral neuromodulation (SNM) system at 6 months. (left) Satisfaction for therapy responders—patients with ≥ 50% improvement in voiding symptoms ($n = 50$). (right) Satisfaction for therapy non-responders—patients with < 50% improvement in voiding symptoms ($n = 16$). ***$P < 0.001$

resolved through selecting good communication and optimizing procedures.

Nearly all patients and physician programmer expressed a high degree of satisfaction with the remote-programming sessions. Patients preferred the remote programming and reported a 92% satisfaction, whereas 83% patients agreed with conventional programming (Fig. 5c). Overall, among the 69 implanted patients, 77% were satisfied with their clinical therapy, and when analyzed for therapy responders, 91% of patients were satisfied with their therapy. For the patients who did not meet the definition for therapeutic success, 21% of patients remained very satisfied with SNM therapy (Fig. 5e).

Discussion

To date, OAB remains a great challenge owing to the available treatments which may either exhibit moderate efficacy or be highly invasive. Consequently, a successful and efficacious long-term therapy is extremely important for the management of refractory OAB. This study is the first randomized controlled study in humans to compare clinical outcomes from a SNM stimulation ON group against a control group for the treatment of OAB. The data from this 6-month phase of the study provided strong scientific

evidence for the benefits of BetterStim system among OAB patients. The overall OAB therapeutic success rate demonstrated high efficiency of SNM for OAB patients after 6 months of treatment. While long-term durability of BetterStim SNM system needs to follow-up until 5 years after implantation. The efficacy of SNM revealed in this trial is comparable with previously reported results of other SNM device [6, 9, 12, 22]. When compared to the patient population of the InSite trial, this cohort of all patients was considered to have severe OAB (≥ 11 voids/day) with a mean of 29.15 voids per day at baseline, which confirms that SNM is equally effective regardless of severity of OAB symptoms [23]. Of the 69 patients with implants, 43 (62%) no longer required combination therapy with medication to improve their OAB symptoms. Besides the objective differences, this study also revealed a significant improvement in subjective measurements. Sustained quality of life improvement was reported from baseline to the 3-month follow-up visit in terms of urinary symptom interference in the treatment group, compared with the control group. Additionally, the high rate of patient satisfaction suggests that patients would benefit from this BetterStim system at 6-months. Overall, these findings reinforce the efficiency of BetterStim system for OAB treatment.

The reported complication rate in this study is significantly lower than previously published studies [9, 12, 24], but must be considered as a matter of therapy evaluation. This may be related to the technologies employed during this study, including the application of tined lead and fluoroscopic guidance for implanting the lead. No serious device-related AE and unanticipated adverse events were reported. The most common device-related AE reported was loss of efficacy in this study. This type of event occurred within 6 months of implant in 4.00% of patients in the InSite study in 7.14% of subjects to date in this study. In this study, the rate of implant site pain was one-third of what was represented in the InSite trial (2.86% vs 8.50%, respectively). Undesirable change in stimulation was also considerably lower in the current trial compared to InSite trial (2.86% vs 10.2%). In both studies, these events were often resolved by medications or complex reprogramming [12, 25]. These data suggest that this novel BetterStim system is safe. Long-term follow-up is needed to determine if the BetterStim system impacts AEs rates.

Notably, patients undergoing SNM therapy often must travel significant distances, which represent a considerable investment on their part of time for a postoperative programming. The ideal solution to the outlined issues lies in wireless and remote-programming technology [26]. With this technology, the need for patients normally required back to hospital in-person is eliminated, thus obviously minimize inconvenience and costs associated with traveling for an in-person clinic visit. Remote programming of implanted SNM system is possible via wireless communication function, thereby enabling patients to receive the same treatment outcomes in their own home as in the hospital. Additionally, the BetterStim system has software controls such that parameter settings would be restored if the signal interrupts. Data for programming from all patients can be stored and analyzed for further investigation and optimization. Therefore, it may revolutionize the management of post-implant patients and allow the development of an applicable and reliable alternative within the market, especially in developing countries.

Although it is vital to report on the efficacy and safety of this novel BetterStim system in the setting of a clinical trial, some limitations need to explored. No previous beta3 adrenoceptor agonist monotherapy and/or its combination with anticholinergic drugs were applied for refractory OAB patients, largely due to beta3 adrenoceptor agonist was not approved for clinical use in China during the trial period. In addition, the definition of refractory OAB was not clearly stated in the inclusion criteria, though all clinical centers recruited patients in terms of suggestion that subjects failed or could not tolerate at least one anticholinergic and have at least one anticholinergic medication not yet attempted. Furthermore, this trial provided 6-month follow-up data without long-term results. This study is an ongoing trial, the quality and long-term duration of treatment benefits will continue to be confirmed. Further investigations will focus on the molecular mechanisms underlying the efficacy of sacral neuromodulation, specifically, the mechanisms by which neuromodulation may affect the functioning of bladder, urethra, sphincter, and other organs that are dominated by the sacral nerve.

Conclusions

This is the first multicenter, prospective, randomized, controlled study testing the efficacy of BetterStim system in OAB subjects. In summary, results from the present study provide strong evidence that this novel remote-programmed SNM system (PINS, Beijing, China) is safe and effective for patients with refractory OAB symptoms. Importantly, our data suggest that remote programming can be safely used as a viable option for the conventional postoperative clinic visit with a high degree of patient satisfaction.

Acknowledgements This work was partially supported by the National Key R&D Program of China (Grant no. 2016YFC0105500) and the National Key R&D Program of China (Grant no. 2018YFC2002200).

Author contributions JYW: protocol/project development, data collection and management, data analysis, and manuscript writing. YGZ: protocol/project development, data collection and management, data analysis, and manuscript writing. LML: protocol/project development, data collection and management, data analysis, and manuscript writing.

PZ: protocol/project development, data collection and management, and data analysis. GQC: protocol/project development and data collection and management. YL: protocol/project development and data collection and management. YZ: protocol/project development and data collection and management. ZQW: protocol/project development and data collection and management. LLM: protocol/project development and data collection and management. XJT: protocol/project development and data collection and management. BKS: protocol/project development, data collection and management. ZHX: protocol/project development and data collection and management. WZ: protocol/project development and data collection and analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All the procedures performed involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. White N, Iglesia CB (2016) Overactive bladder. Obstet Gynecol Clin North Am 43(1):59–68. https://doi.org/10.1016/j.ogc.2015.10.002
2. Eapen RS, Radomski SB (2016) Review of the epidemiology of overactive bladder. Res Rep Urol 8:71–76. https://doi.org/10.2147/RRU.S102441
3. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, Hunt TL, Wein AJ (2003) Prevalence and burden of overactive bladder in the United States. World J Urol 20(6):327–336. https://doi.org/10.1007/s00345-002-0301-4
4. Ruffion A, Castro-Diaz D, Patel H, Khalaf K, Onyenwenyi A, Globe D, Lereun C, Teneishvili M, Edwards M (2013) Systematic review of the epidemiology of urinary incontinence and detrusor overactivity among patients with neurogenic overactive bladder. Neuroepidemiology 41(3–4):146–155. https://doi.org/10.1159/000353274
5. Wang Y, Xu K, Hu H, Zhang X, Wang X, Na Y, Kang X (2011) Prevalence, risk factors, and impact on health related quality of life of overactive bladder in China. Neurourol Urodyn 30(8):1448–1455. https://doi.org/10.1002/nau.21072
6. Siegel S, Noblett K, Mangel J, Griebling TL, Sutherland SE, Bird ET, Comiter C, Culkin D, Bennett J, Zylstra S, Berg KC, Kan F, Irwin CP (2015) Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. Neurourol Urodyn 34(3):224–230. https://doi.org/10.1002/nau.22544
7. Amundsen CL, Richter HE, Menefee SA, Komesu YM, Arya LA, Gregory WT, Myers DL, Zyczynski HM, Vasavada S, Nolen TL, Wallace D, Meikle SF (2016) Onabotulinumtoxin A vs sacral neuromodulation on refractory urgency urinary incontinence in Women: a randomized clinical trial. JAMA 316(13):1366–1374. https://doi.org/10.1001/jama.2016.14617
8. Tang H, Chen J, Wang Y, Yu T, Guo C, Liao X (2014) Combination of sacral neuromodulation and tolterodine for treatment of idiopathic overactive bladder in women: a clinical trial. Urol J 11(4):1800–1805
9. Siegel S, Noblett K, Mangel J, Bennett J, Griebling TL, Sutherland SE, Bird ET, Comiter C, Culkin D, Zylstra S, Kan F, Berg KC (2018) Five-year followup results of a prospective, multicenter study of patients with overactive bladder treated with sacral neuromodulation. J Urol 199(1):229–236. https://doi.org/10.1016/j.juro.2017.07.010
10. Braun PM, Bohler G (2006) Results of sacral nerve modulation for treatment of overactive bladder. Urologe A 45(7):835–840. https://doi.org/10.1007/s00120-006-1085-8
11. Matzel KE, Stadelmaier U, Hohenfellner M, Gall FP (1995) Electrical stimulation of sacral spinal nerves for treatment of faecal incontinence. Lancet 346(8983):1124–1127
12. Blok B, Van Kerrebroeck P, de Wachter S, Ruffion A, Van der Aa F, Jairam R, Perrouin-Verbe M, Elneil S (2018) Three month clinical results with a rechargeable sacral neuromodulation system for the treatment of overactive bladder. Neurourol Urodyn 37(S2):S9–S16. https://doi.org/10.1002/nau.23465
13. Elterman DS (2018) The novel axonics (R) rechargeable sacral neuromodulation system: procedural and technical impressions from an initial North American experience. Neurourol Urodyn 37(S2):S1–S8. https://doi.org/10.1002/nau.23482
14. Chen Y, Hao H, Chen H, Tian Y, Li L (2014) The study on a real-time remote monitoring system for Parkinson's disease patients with deep brain stimulators. Conf Proc IEEE Eng Med Biol Soc 2014:1358–1361. https://doi.org/10.1109/EMBC.2014.6943851
15. Hwa K, Wren SM (2013) Telehealth follow-up in lieu of postoperative clinic visit for ambulatory surgery: results of a pilot program. JAMA Surg 148(9):823–827. https://doi.org/10.1001/jamasurg.2013.2672
16. Chen Y, Hao H, Chen H, Li L (2015) The study on a telemedicine interaction mode for Deep Brain Stimulation postoperative follow-up. Conf Proc IEEE Eng Med Biol Soc 2015:186–189. https://doi.org/10.1109/EMBC.2015.7318331
17. Zhang C, Li D, Zeljic K, Tan H, Ning Y, Sun B (2016) A remote and wireless deep brain stimulation programming system. Neuromodulation 19(4):437–439. https://doi.org/10.1111/ner.12448
18. Schulz KF, Altman DG, Moher D, Group C (2010) CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med 8:18. https://doi.org/10.1186/1741-7015-8-18
19. Chancellor MB, Migliaccio-Walle K, Bramley TJ, Chaudhari SL, Corbell C, Globe D (2013) Long-term patterns of use and treatment failure with anticholinergic agents for overactive bladder. Clin Ther 35(11):1744–1751. https://doi.org/10.1016/j.clinthera.2013.08.017
20. Matzel KE, Chartier-Kastler E, Knowles CH, Lehur PA, Munoz-Duyos A, Ratto C, Rydningen MB, Sorensen M, van Kerrebroeck P, de Wachter S (2017) Sacral neuromodulation: standardized electrode placement technique. Neuromodulation 20(8):816–824. https://doi.org/10.1111/ner.12695
21. Coyne K, Revicki D, Hunt T, Corey R, Stewart W, Bentkover J, Kurth H, Abrams P (2002) Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. Qual Life Res 11(6):563–574
22. Siegel S, Noblett K, Mangel J, Griebling TL, Sutherland SE, Bird ET, Comiter C, Culkin D, Bennett J, Zylstra S, Kan F, Thiery E (2016) Three-year follow-up results of a prospective, multicenter study in overactive bladder subjects treated with sacral neuromodulation. Urology 94:57–63. https://doi.org/10.1016/j.urology.2016.04.024
23. Noblett K, Berg KC, Kan F, Siegel S (2018) Baseline symptom severity and therapeutic success in a large prospective trial of sacral neuromodulation therapy for overactive bladder patients.

Neurourol Urodyn 37(5):1667–1671. https://doi.org/10.1002/nau.23422
24. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, Lycklama a Nijholt AA, Siegel S, Jonas U, Fowler CJ, Fall M, Gajewski JB, Hassouna MM, Cappellano F, Elhilali MM, Milam DF, Das AK, Dijkema HE, van den Hombergh U (2007) Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol 178(5):2029–2034. https://doi.org/10.1016/j.juro.2007.07.032
25. Noblett K, Benson K, Kreder K (2017) Detailed analysis of adverse events and surgical interventions in a large prospective trial of sacral neuromodulation therapy for overactive bladder patients. Neurourol Urodyn 36(4):1136–1139. https://doi.org/10.1002/nau.23076
26. McElveen JT Jr, Blackburn EL, Green JD Jr, McLear PW, Thimsen DJ, Wilson BS (2010) Remote programming of cochlear implants: a telecommunications model. Otol Neurotol 31(7):1035–1040. https://doi.org/10.1097/MAO.0b013e3181d35d87

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Affiliations

Yaoguang Zhang[1,9] · Peng Zhang[2] · Xiaojun Tian[3] · Guoqing Chen[4] · Yan Li[5] · Yong Zhang[6] · Zhihui Xu[7] · Zhongqing Wei[8] · Wei Zhang[1,9] · Lulin Ma[3] · Benkang Shi[5] · Limin Liao[4] · Jianye Wang[1,9]

1 Urology Department, Beijing Hospital, National Center of Gerontology, No. 1 DaHua Road, Dong Dan, Beijing 100730, People's Republic of China

2 Urology Department, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, People's Republic of China

3 Urology Department, Peking University Third Hospital, Beijing 100191, People's Republic of China

4 Urology Department, China Rehabilitation Research Center, Capital Medical University, No. 10 North Road, Fengtai District, Beijing 100068, People's Republic of China

5 Urology Department, Qilu Hospital, Shandong University, Jinan, Shandong 250012, People's Republic of China

6 Urology Department, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, People's Republic of China

7 Urology Department, Zhejiang Provincial People's Hospital, Hangzhou, Zhejiang 310014, People's Republic of China

8 Urology Department, Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210000, People's Republic of China

9 Peking University Fifth School of Clinical Medicine, Beijing 100730, People's Republic of China