Received: 7 February 2019 | Revised: 2 April 2019 | Accepted: 17 April 2019

DOI: 10.1002/nau.24035

ORIGINAL CLINICAL ARTICLE

First-in-human implantation of a mid-field powered neurostimulator at the sacral nerve: Results from an acute study

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Abstract

Introduction: Commercially approved implantable systems for sacral neuromodulation require the implantation of a multipolar lead subcutaneously connected to an implantable pulse generator (IPG). Eliminating the need for an IPG would eliminate the need for tunneling of the lead, reduce procedure time, infection risk, and the need for IPG replacement. The objective was to demonstrate the feasibility of implanting the AHLeveeS System in the S3 Foramen to stimulate the S3 sacral nerve.

Materials and Methods: A first-in-human, prospective, single center, nonrandomized, acute feasibility clinical investigation at the Maastricht University Medical Center+. Patients with refractory overactive bladder underwent acute implantation of the AHLeveeS neurostimulator before the InterStim procedure. Outcome measurements included motor responses, procedural time and a scoring of the difficulty of the implant and explant procedure. Retrospectively, qualitative responses to the stimulation protocol were assessed by video motion analyses. Only descriptive statistics were used.

Results: During the stimulation a motor response to stimulation was seen in four of the five subjects. In all implantations the AHLeveeS was correctly placed. The median time for complete procedure was 24 minutes. The implant and explant procedures were successfully performed and no device or procedure related adverse events occurred.

Conclusions: The results from this acute first-in-human study demonstrate the feasibility of implantation and acute stimulation of the sacral nerve with this mid-field powered system. Future clinical studies will focus on safety and efficacy of a chronically implanted device.

KEYWORDS

first-in-human, incontinence, overactive bladder, sacral neuromodulation

1 | INTRODUCTION

Overactive bladder (OAB) is defined by the International Continence Society as urinary urgency in the absence of any known infection or other obvious pathology. OAB is usually characterized by frequency and nocturia, and may or may not be associated with urgency urinary incontinence. Millions of patients worldwide are

annually diagnosed with OAB and associated urinary incontinence, with an estimated 546 million patients with OAB by 2018.[1]

First-line treatment includes noninvasive behavioral therapies such as bladder training, fluid management, and pelvic floor muscle training. When symptoms do not adequately improve with first-line treatment, second-line treatment includes combined behavioral and pharmacologic therapies including antimuscarinics and β-receptor agonists. Third-line treatments include bladder chemodenervation with onabotulinum toxin injections or neuromodulation.

Implantable sacral nerve stimulation (SNS) systems such as the Medtronic InterStim II (Medtronic Inc., Minneapolis, MN) consists of a 28 cm lead with a distal quadripolar electrode array positioned in the S3 Foramen with a proximal connecting section that is tunneled to a pulse generator (14 cm^3) in a subcutaneous pocket that is typically located above the buttocks. This system has demonstrated a 5-year efficacy of 82% for the treatment of urgency incontinence and urgency/frequency.[2] However, the benefits of a completely implantable SNS system come with a substantial set of complications, affecting 30% of subjects. The most common complications include implantable pulse generator (IPG) site pain or infection, battery depletion, lead migration, lack of efficacy, and device erosion, with an associated surgical reintervention rate of 13% over 5 years.[3]

Implantable neuromodulation systems require the placement of a multipolar lead located near the target nerve for stimulation with the proximal section tunneled subcutaneously to the IPG. A highly miniaturized implantable stimulator without a long implantable lead and without the need for an IPG would facilitate a less invasive implantation approach. Avoiding IPG placement and the associated subcutaneous lead tunneling would reduce the incremental operative cost. A battery-free system eliminates the risk of IPG infection and generator pocket discomfort, and could reduce the rate of lead migration.

As an alternative to the currently available SNS system, Neuspera Medical Inc (San Jose, CA) developed the AHLeveeS System. This is a minimally invasive system consisting of a miniature implantable stimulator and proprietary wireless mid-field powering unit (total length of device = 4 cm, volume = 0.05 cm^3) that is percutaneously positioned in the S3 Foramen. Midfield powering is a method for wirelessly transferring power from an external powering unit to highly miniaturized electronic devices implanted deep in the body.[4] The AHLeveeS System was designed and qualified solely for use in the clinical investigation described here.

2 | OBJECTIVE

The purpose of this clinical investigation was to demonstrate the feasibility of implanting the AHLeveeS System in the S3 Foramen to stimulate the S3 sacral nerve. The primary objectives of the clinical investigation were to verify that energy could be transmitted from an external unit to the implanted stimulator, through a wireless connection, resulting in stimulation of the S3 sacral nerve, and to confirm that the implantable stimulator could be correctly placed in close proximity of the sacral nerve, in the S3 foramen. Furthermore, the study aimed to characterize the explant of the device following the intraoperative stimulation.

3 | MATERIALS AND METHODS

A first-in-human, prospective, single center, nonrandomized, acute feasibility clinical investigation was approved at the Maastricht University Medical Center+ (ClinicalTrials.gov identifier: NCT03643380). The investigation was conducted in adherence to the latest version of the Declaration of Helsinki, a predefined clinical investigation plan, requirements of the approving ethics committee and competent authorities, ISO 14155, Medical Devices Directive 93/42/EEC Annex X—Clinical Evaluation, and other applicable regional and national regulatory requirements. Subject enrollment started in August 2017 and the clinical investigation was completed in December 2017.

3.1 | Study population

The investigation aimed to enroll five to 10 subjects at one investigational center. Subjects were considered enrolled in the clinical investigation after they provided written informed consent. Included subjects (with standard indication of refractory OAB) were offered participation in the acute trial if they were already eligible for the Interstim procedure, in good general health, able to understand the study and willing to provide informed consent, and a minimum 18 years of age to a maximum 65 years of age.

3.2 | Devices and implant tools

The distal section of the implantable stimulator contains a quadripolar array with physical dimensions similar to its commercially available counterpart. The 4-electrodes (90/10 platinum-iridium alloy) are each 1.33 mm in diameter × 3 mm long, equally spaced at 3 mm, with a 1.33 diameter thermoplastic elastomer insulator. This

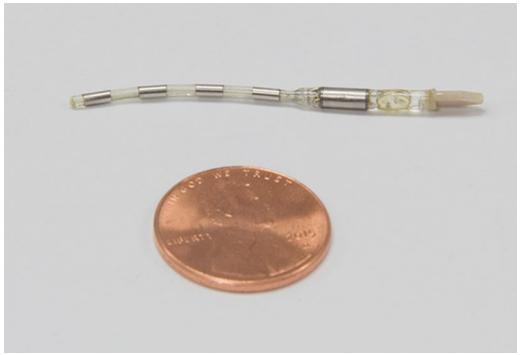

FIGURE 1 Implantable stimulator

section has a 4 F diameter transitioning to a 7 F proximal section diameter containing the energy harvesting electronics and a stimulation circuit within a hermetic enclosure. There is no implantable battery power source. The implantable stimulator is approximately 4 cm in length with a displacement volume less than 0.05 cm^3 (Figure 1). A suture is attached to the proximal section of the device to facilitate retrieval.

The implantable stimulator was implanted percutaneously using the standard S3 foramen needle localization technique that occurs with commercially available system placement, followed by dilation of the foramen utilizing a conventional dilator and sheath for passage of the AHLeveeS device into the sacral neuroforamen. A stainless steel push rod keyed to the proximal end of the implantable stimulator allowed for axial positioning within the neuroforamen.

The external powering unit was contained within in a sterile drape and it was centered above the S3 Foramen entrance. The external unit was housed in a 10 cm plastic enclosure that contained the Mid-Field Powering circuits, antenna and a rechargeable battery (Figure 2).

3.3 | Interventions

Following general anesthesia without using long acting muscle relaxants, the patient was brought into prone position and S3 and S4 Foramina were landmarked. A 20 G foramen needle was inserted approximately 2 cm cephalad to the sacroiliac joints and 2 cm lateral to the sacral midline. Using fluoroscopy, the insulated needle was inserted into the foramen with an approximate 60° insertion angle relative to the skin using a modified Seldinger technique. The sacral nerves (in all individuals the S3) were stimulated with standard settings of pulse width 210 ms, rate 14 Hz, at amplitudes ranging between 0.5 and 5 V. Stimulation thresholds were identified while observing bellows response and great toe flexion response. The device was implanted and the correct position was confirmed using fluoroscopy.

FIGURE 2 Internal view of external powering unit

The stimulation protocol was then started and the motor reaction at the level of the anal area and the foot were monitored by video motion. The stimulator frequency was a nominal 10 Hz and the amplitude at the electrode was 2.4 V. Stimulation was bipolar, with lead most proximal lead as the anode and the most distal lead as the cathode. The external unit was packed in a sterile bag and held over the implantation site. Physiological responses were recorded when the external unit was turned on. When no physiological responses were observed, the external unit (set at 2.4 V) was slowly moved around the implantation site until a response was seen. The device was then explanted by pulling the proximal suture in the same direction as the implant path, followed by standard SNS tined lead electrode implantation. Subjects were followed for 30 days (±5 days) after the study treatment procedure.

3.4 | Outcome measurements and statistical analysis

During foramen needle placement, functional mapping was performed to analyze whether an anal bellows and/or great toe response to stimulation could be observed. Intraoperative outcome measures included motor responses and procedural time. Furthermore, the investigator was asked to score the difficulty of the implant and explant procedure (very easy/easy/neutral/difficult/very difficult) and to assess whether the device could be correctly placed. Retrospectively, qualitative responses to the stimulation protocol of the bellow and great toe were

assessed by the investigator by video motion analyses (none/marginal or unclear/obvious).

No statistical sample size calculations were performed as this was a proof of concept study. The clinical investigation was designed as a small acute proof of concept study and results were not sufficient to show any statistical significance. Thus no statistical hypothesis testing was performed. Only descriptive statistics (mean, standard deviation, and changes from baseline) were used.

4 | RESULTS

4.1 | Baseline and demographic characteristics

A total of six subjects were enrolled. A total of five subjects underwent the study procedure and one subject withdrew consent before surgery. All five subjects completed the study without any protocol deviations. Of the five subjects, one was male (20%) and four were female (80%). The mean age of the treated subjects was 46.4 ± 17.6 years (range 21-65 years). The mean body mass index was 27.1 ± 3.9 kg/m^2 (range 21.2-31.8 kg/m^2).

4.2 | Physiological responses

Visual physiologic responses to the stimulation procedure were observed in four of five subjects (80%). Each of these subjects showed an anal bellows response, and three demonstrated flexion of the big toe during stimulation. In the four subjects with appropriate motor response, stimulation thresholds were less than 1.5 V. The subject not responding to stimulation had a high minimal threshold (5 V) during functional mapping exceeding the 2.4 V stimulation voltage of the AHLeveeS System. This individual also proved to be a nonresponder to the InterStim device. The other four subjects had a minimal threshold less than 1 V (one subject) or exactly 1 V (three subjects).

The investigator assessed the anal bellows motion as "obvious" in four out of five subjects (80%) and "none" in one (20%). The investigator assessed the toe flex motion to be "obvious" for three out of five subjects (60%) and "none" in two subjects (40%). An overview of physiological response is provided in Table 1.

4.3 | Device positioning

The device could be correctly placed with fluoroscopic confirmation of proper device positioning with the most proximal electrode at the anterior surface of S3 in all five subjects (100%) (Figure 3). The investigator assessed the implant procedure to be "very difficult" in one case. This was for the subject that did not have any observed responses. The procedure was assessed as "very easy" in two cases and as "easy" in two cases. Successful stimulation with the EPU was accomplished by moving the EPU within an approximately 5 cm radius around the implant site.

TABLE 1 Physiologic response observation summary

Stimulation protocol performed accurately		
Yes	*N*	4
	%	80
No	*N*	1
	%	20
Could any visual response be observed		
Yes	*N*	4
	%	80
No	*N*	1
	%	20
Anal bellows response observed		
Yes	*N*	4
	%	80
No	*N*	1
	%	20
Twitching of big toe response observed		
Yes	*N*	3
	%	60
No	*N*	2
	%	40
Movement in other toes response observed		
Yes	*N*	3
	%	60
No	*N*	2
	%	40
Other physiologic response observed		
Yes	*N*	0
	%	0
No	*N*	5
	%	100

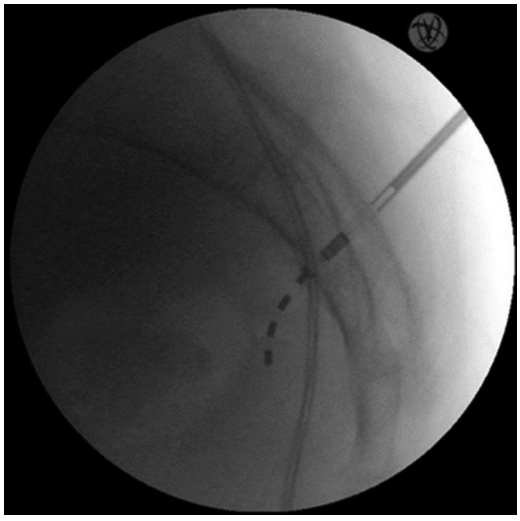

FIGURE 3 Fluoroscopic image of stimulator with the implant tool

4.4 | Procedure time

The median time from first incision until explant procedure was 24 minutes. The elapsed time between the end of the stimulation protocol and the moment the device was explanted from the body was on average 0.2 minutes and maximal 1 minute. An overview of the procedure time is provided in Table 2.

4.5 | Explant procedure

The explant procedure was assessed as being performed successfully and as "very easy" for all five subjects treated. The implant and explant of the experimental device did not adversely affect the InterStim stimulation.

4.6 | Safety events

During the course of the clinical investigation, three adverse events occurred in three subjects. None of the adverse events were assessed as device related or procedure related, and none were reported to be "serious."

Two subjects presented with a urinary tract infection which was treated with antibiotics; and one subject presented with adverse change in bowel or voiding function, and undesirable stimulation or sensation from the InterStim implant, and it was resolved without medical intervention.

5 | DISCUSSION AND CONCLUSIONS

SNS using the commercially available system is prescribed for the treatment of OAB in patients that have failed or could not tolerate more conservative treatments. Test stimulation is associated with success rates approximating 70%[5] followed by a success rates more than 80% after IPG implantation.[6] However, the benefits of the commercially available system come with a set of drawbacks. Device-related complications associated with the commercially available system include lead migration, fracture, pocket infection, lead infection, pocket pain, and cosmetic issues including a bulge above the

TABLE 2 Elapsed procedure time summary

Time first incision to implant NSM AHLeveeS System (min)	
N	5
Mean	13.2
Std	8
Min	4
Max	25
Median	14
Time implant NSM AHLeveeS System to first visual response (min)	
N	4
Mean	1.5
Std	0.6
Min	1
Max	2
Median	2
Time first visual response to end of stimulation protocol (min)	
N	4
Mean	1.5
Std	1.3
Min	0
Max	3
Median	2
Time end of stimulation protocol to explant NSM AHLeveeS System (min)	
N	5
Mean	0.2
Std	0.4
Min	0
Max	1
Median	0
Time first incision to explant NSM AHLeveeS System (min)	
N	5
Mean	27.4
Std	31.3
Min	8
Max	83
Median	17

buttocks.[3] Similar drawbacks can be considered with the use of rechargeable SNS systems that are currently undergoing clinical trials.[7] The AHLeveeS System was developed to demonstrate the feasibility of an alternative to currently available implantable SNS systems. The lack of an externalized test lead and the lack of an IPG could lower the risk of infection. Furthermore, absence of a of an externalized lead during a trial (stage I) procedure and no need for connection to a pulse generator may also lower rate of proximal lead migration.

The primary objective of this clinical investigation was to verify that energy could be transmitted from an external unit through a wireless connection resulting in stimulation of the S3 sacral nerve. Physiological responses were measured as great toe flexion and bellows response. These are the typical motor responses related to the sacral nerve, as outlined for example by Cohen et al.[8] The results of this clinical investigation confirmed that qualitative and quantitative physiological responses to stimulation with the system can be obtained and it was able to transmit its energy to the S3 sacral nerve in an effective manner.

One of five subjects did not respond to stimulation of the S3 sacral nerve with either needle stimulation (nerve mapping) or system stimulation. The absence of a motor response upon direct SNS is not uncommon and has previously been described in the literature (86%-95% motor response rate[8,9]). Absence of observation of a motor response does not necessarily indicate that the use of the stimulator will prove ineffective for these subjects; sensory responses may be recorded while motor responses are absent, and outcomes may prove successful.[9] Nor does successful sensory and motor responses guarantee successful clinical outcome. In this study, the standard of care SNS device that the subject had implanted after the study procedure turned out to be unsuccessful. It is therefore suggested that the absence of a qualitative and quantitative physiological response in this subject was not related to a malfunction or an insufficiency in the system, but rather to intrinsic nonresponsiveness of the S3 root.

The secondary objective of this clinical investigation was to confirm that the implant could be correctly placed and inserted in close proximity to the sacral nerve, via the S3 Foramen. Positioning proved to be correct for all subjects. It can be concluded that the design of the system allows for functional placement of the device into the human body.

The device explant procedure was considered relevant for the appraisal of the device, as device explant may be required on patient request, if the patient symptoms have dramatically improved, or in case of malfunctioning or adverse body reactions. The device explant procedure was assessed as very easy, successful, and within normal expected times. While acute explantation was easy and successful, the device has not yet been tested in humans for ease of removal of a chronically implanted device. However, animal studies have demonstrated straightforward explantation at 90 days.

No device related adverse events, procedure related adverse events, or any device deficiencies occurred during the course of the clinical investigation. The study results show that the system was safe to use during implant, stimulation and explant. It should be noted that the safety of the device was only tested during the very brief time of stimulation, and not in a chronic setting. Device related complications such as those reported for the commercially available system could not be assessed as part of this study.

This study was limited to acute implantation and explantation. One should not draw any conclusions with respect to the safety and performance of this system in a chronic setting. The main aim of the study to demonstrate the feasibility of implantation, and stimulation of the sacral nerve in the S3 Foramen, was confirmed. Future studies will focus on safety, implant stability, and efficacy in an ambulatory setting.

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How to cite this article: van Kerrebroeck PEVA, Reekmans M, van Koeveringe GA, et al. First-in-human implantation of a mid-field powered neurostimulator at the sacral nerve: Results from an acute study. *Neurourology and Urodynamics*. 2019;1-7. https://doi.org/10.1002/nau.24035