Feasibility of Long-term Tibial Nerve Stimulation Using a Multi-contact and Wirelessly Powered Neurostimulation System Implanted in Rats

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OBJECTIVE Implant-driven tibial nerve stimulation therapy is an effective technique for treating overactive bladder. However, the monopolar lead design in the currently available implantable devices pose long-term therapeutic challenges in terms of efficiently and selectively delivering electrical pulses to the target. Hence, the purpose of this study was to (1) characterize the tibial nerve (TN) activation properties using a multi-contact implantable system and (2) evaluate the long-term stability of using such a neural interface in a preclinical model.

MATERIALS AND METHODS Ten adult Sprague-Dawley rats were used in this study. An implantable pulse generator was surgically inserted in the lower back region. The lead wire with 4 active electrodes was placed in parallel with the TN. The threshold for activating the TN was confirmed via movement of the hallux or toes as well as the foot EMG. The TN activation threshold was assessed biweekly, over a period of 12 weeks.

RESULTS Channel 1 exhibited the lowest motor threshold at T_0 (mean = 0.58 ± 0.10 mA). A notable increase in motor twitch intensity was observed during the first test session (2 weeks) following surgical implantation (75.8 ± 30.5%, channel 1). Among the 10 rats tested, 8 rats successfully completed the 3-month study.

CONCLUSION Results from this study demonstrate the long-term feasibility of achieving tibial nerve stimulation with a multi-contact implantable device in a preclinical model. Future studies are warranted to assess the effects of using such a wirelessly powered system for treating lower urinary tract symptoms in patients. UROLOGY 102: 61–67, 2017. © 2016 Elsevier Inc.

Overactive bladder (OAB) is a chronic medical condition that is defined by episodes of urinary urgency, frequency, and incontinence.[1] Affecting approximately 16% of the adult population worldwide,[2] the stigmatizing effects of OAB can significantly impact the quality of life of an individual. Various treatment algorithms such as pharmacotherapies (ie, antimuscarinic drugs) are used to suppress OAB symptoms; however, patient compliance is often limited because of secondary side effects (eg, dry mouth and nausea).[3] As an effective alternative, sacral nerve stimulation (SNS) can be used to significantly improve lower urinary tract symptoms, such as urinary frequency, urge incontinence, and even urinary retention.[4,5] However, because the bladder-inhibitory effects of SNS rapidly diminish following termination of the stimulus,[6] electrical stimulation must be provided on a continuous basis and thereby requires a surgically implanted pulse generator located in the sacral spinal region. Myriad issues such as stimulation-evoked side effects (eg, leg movement), lead migration, electrode breakage, and periodic battery replacement preclude SNS as a first or second line of treatment for OAB.

Percutaneous tibial nerve stimulation (PTNS) therapy is a significantly less-invasive treatment option that—unlike SNS—does not require continuous electrical stimulation.[7,8,9] The therapy involves weekly visits to the clinic, during which a percutaneously inserted needle electrode is used to activate the tibial nerve (TN). Each session requires only 30 minutes of electrical stimulation, where the amplitude is set at approximately the foot motor threshold. The standard treatment period lasts for 12 weeks

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followed by maintenance sessions repeated every 3 weeks thereafter.[10,11] Although clinical trials show significant improvements in OAB symptoms, long-term patient compliance is a noted limitation.[12,13] Whether this is due to discomfort caused by nerve stimulation, logistic issues associated with repeated visits to the clinic, or even loss of treatment effectiveness, there is a need for improving long-term therapeutic efficacy.

Implantable neurostimulation devices offer a major advantage over the current PTNS paradigm, as these devices can enable patients to maximize therapeutic efficacy through self-administered treatment. Not only could implantable neurostimulation devices facilitate more frequent stimulation sessions and hence, more rapid induction of therapy,[14-16] but it could also enable patients to customize stimulation parameters to better sustain long-term efficacy. To date, the Urgent SQ system is the only chronically implanted device that has been clinically tested for treating OAB symptoms.[17,18] Among the 8 patients that were enrolled in this study—all of whom were positive PTNS responders before implantation[19]—only 3 patients continued to use the device at 9 years post implant. It is interesting to note that while electrical activation of the TN was confirmed intraoperatively in every patient, stimulation-evoked motor and sensory responses (at 9 years post implant) were achieved in only these 3 individuals. The eventual loss of motor and sensory responses among the "negative responders" suggests that the monopolar lead design used in the Urgent SQ system was unable to achieve consistent electrical activation of the TN.

In the present study, we investigated the feasibility of using a multi-contact electrode array as a means of achieving stable long-term electrical activation of TN. As described in a previous study,[20] the electrode array is connected to an implantable pulse generator (IPG) (Gecko system) that is powered externally via radiofrequency energy. The system can be programmed to deliver electrical pulses through any 1 of the 4 electrode contacts. The goals of this preclinical study were (1) to characterize the nerve activation properties of the multi-contact Gecko system and (2) to evaluate the long-term performance of this implanted system by measuring the TN activation threshold over a period of 3 months.

MATERIALS AND METHODS

All experimental protocols were approved by the Animal Use Committee at the University of Toronto in accordance with the Ontario Animal Research Act (Toronto, Ontario, Canada).

Wireless Stimulation System

A wireless nerve stimulator (Gecko 1.0; Nuviant Medical Inc., Dallas, TX; Fig. 1A) was used in the present study. The prototype system consists of an IPG, an electrode lead, and an external transmitter connected via USB to a computer running the programming software (Fig. 1B). The IPG consists of a M24LR16E dynamic NFC/RFID tag integrated circuit (STMicroelectronics; Geneva, Switzerland), a MSP430 microcontroller (Texas Instruments, Dallas, TX), and a CSI021 programmable current source (Cactus Semiconductor, Chandler, AZ). The implanted system was programmed in the current study to output monophasic cathodic square pulse waveforms, 200-microsecond pulse width, 20-second pulse train duration, 6-Hz pulse frequency, and stimulation amplitudes up to 5 mA. The IPG served as the electrode return. The implanted device was powered by radiofrequency energy that was transmitted between the aligned external transmitter and internal receiving coils. Electrical pulses generated by the IPG were sent to 1 of the 4 electrode contacts located at the end of the lead wire (length = 15 cm, diameter = 1.29 mm). Each circumferential electrode contact was 1.25 mm in length and separated from an adjacent contact by 2 mm.

Implantation Procedure

The stimulating device was surgically implanted in 10 male Sprague-Dawley rats (mean weight = 500-800 g) under sterile conditions. The animal was anesthetized by inhaled isoflurane (3%-5%, O_2 level: 1.0 L/min) and maintained throughout the procedure. Anesthetic levels were monitored by arterial SpO_2 level, heart rate (300-350 bpm), respiration rate, and toe pinch reflex. Body temperature was maintained by a heating pad set at 42°C. Before incision, a bolus of ketoprofen (SQ, 5 mg/kg) was administered.

Following an initial incision (3 cm, Fig. 1C) in the upper back, a subcutaneous pocket was created by blunt dissection of the underlying connective tissue. The implantable stimulator (2.5 cm × 4.5 cm) was inserted and anchored with 6-0 suture to the surrounding connective tissue. The lead wire was tunneled subcutaneously with a trocar and exited through a second incision (1 cm, Fig. 1D) made in the lower abdominal area. The lead wire was loosely sutured to the connective tissue underneath the second incision. A third incision (2 cm, Fig. 1D) was made along the medial aspect of the lower leg, which provided surgical access to the TN immediately cephalad to the medial malleolus. The lead wire was then tunneled subcutaneously between the second and third incisions, and positioned such that contacts 1 and 2 were adjacent to the TN (Fig. 1E). The lead wire was sutured to connective tissue surrounding the TN at the site of the third incision. All incision sites were sutured closed (4-0 suture), rinsed with sterile saline, and dressed with antibiotic ointment. The threshold for TN activation (T) was determined by visual confirmation of foot motor responses (eg, hallux, toes, or flexor digitorum brevis) that were evoked in response to electrical pulses generated by the IPG. The nerve activation threshold was measured for all 4 electrode contacts at the time of implantation (T_0, week 0). The animal was monitored following surgery, and supplemental doses of ketoprofen were administered every 24 hours for up to 2 days post implantation.

Electrode Testing Protocol

The threshold for TN activation was re-tested at predetermined time points: weeks 2, 4, 6, 8, and 10 post implant (Fig. 2A). During each testing session, the animal was anesthetized by isoflurane (2%-3%) and key physiological parameters were monitored (heart rate, SPO_2, and respiratory rate). The threshold for activating TN was determined for each of the 4 electrode contacts. At the end of each test procedure, the anesthesia was discontinued and the animal was allowed to recover.

Terminal Study

At week 12, a final test of the foot twitch threshold was conducted. The foot (ipsilateral to the implant) was instrumented with a pair of stainless steel wires (A-M Systems, Carlsborg, WA): (1) one inserted between the hallux and the long digit and (2) the other inserted near the midpoint along the foot (ie, flexor