A Review of Oscillating Field Stimulation to Treat Human Spinal Cord Injury

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Key words
- Oscillating field stimulation
- Spinal cord injury
- Spinal cord injury treatment

Abbreviations and Acronyms
ANOVA: Analysis of variance
NASCIS: National Acute Spinal Cord Injury Study
OFS: Oscillating field stimulator
SCI: Spinal cord injury
SSEP: Somatosensory evoked potential
VAS: Visual analog scale

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OBJECTIVE: **To report the results of use of a human oscillating field stimulator (OFS) in a phase 1 trial of 14 human patients with complete motor and sensory spinal cord injury.**

METHODS: **Entry criteria were complete spinal cord injury between C5 and T10 in patients 18–65 years old with no transection on magnetic resonance imaging. All patients received the National Acute Spinal Cord Injury Study III methylprednisolone protocol. Cord compression or instability was treated before entry. All patient injuries remained complete (based on American Spinal Cord Injury scoring) with no somatosensory evoked potentials (SSEPs) below the injury after surgery or for 48 hours. All patients were implanted with the OFS within 18 days. Patients were checked every 2 weeks after implantation. The OFS was explanted at 15 weeks. Independent neurologic examinations (American Spinal Cord Injury score, visual analog scale for pain, and SSEPs) were done at 6 weeks, 6 months, and 1 year. Statistical analyses were done by Wilcoxon rank sum test and analysis of variance (ANOVA).**

RESULTS: **There were no complications at insertion, and one wound infection occurred after explant for a 3.5% infection rate. One patient was lost to follow-up after 6 months. All 14 patients had a mean visual analog scale score of 8 at implant and 2 at 6 months, and 13 remained a mean score of 2 at 1 year. Mean improvement in light touch score at 1 year was 25.9 points (ANOVA, $P < 0.001$; Wilcoxon, $P = 0.02$). Mean improvement in pinprick score at 1 year was 15.2 points (ANOVA, $P < 0.001$; Wilcoxon, $P = 0.02$). Mean improvement in motor score was 6.9 (ANOVA, $P < 0.01$; Wilcoxon, $P = 0.02$). Of eight patients with cervical cord injuries, six had improvement in arm SSEPs, and one recovered a tibial SSEP. Of six patients with thoracic injuries, one recovered an abnormal lower SSEP.**

CONCLUSIONS: **Treatment of human spinal cord injury with an OFS is safe, reliable, and easy. Compared with National Acute Spinal Cord Injury Study III compliant paralyzed patients, our results suggest efficacy.**

INTRODUCTION

Numerous investigators have documented a naturally occurring voltage gradient of 500–1000 mV/mm that exists in the wall of the early neural tube in vertebrates and is required for guiding cranial-to-caudal nervous system development (5, 13, 26, 27). It has been documented that an applied voltage gradient of 10–500 mV/mm instantly directed the growth of neurites projecting from a single frog neuroblast toward the cathode (negative pole) (12, 14, 16-19, 22, 28). The growth rate of the neurite was increased twofold to threefold in fibers turned toward the cathode. The growth rate was dependent on the magnitude of the imposed fields with the most marked responses occurring between 70 and 140 mV/mm. McCaig and others (6, 15, 23) demonstrated that mammalian neurons in culture showed similar responses. It appears that neurites are programmed to respond to electrical guidance clues during development, and this response may be preserved when axons regenerate after injury. It has been demonstrated in an in vivo severed lamprey spinal cord that an implanted cathode reduced axonal degradation and facilitated functional axonal regeneration toward the cathode (2, 24, 29).

In a mammalian model of spinal cord injury (SCI) using the rat and guinea pig, the application of an electrical field of 400 μV/mm for 3 weeks facilitated axonal regeneration histologically and led to functional improvement as measured by a cutaneous truncal muscle reflex (1, 3, 4). The cathode was placed rostral to the injury, and only sensory recovery was demonstrated. Additionally, these studies showed a reduction in the number of astrocytes at the level of SCI and that the astrocytes oriented their processes parallel to the electrical field reducing glial scar (11, 20, 30).

The placement of a cathode rostral or caudal to SCI would facilitate regeneration in only one direction. To facilitate regeneration for rostrally directed sensory fibers and caudally directed motor fibers, a stimulator was created that would oscillate polarity every 15 minutes. A stimulator was designed with humans in mind but was tested first in a dog with

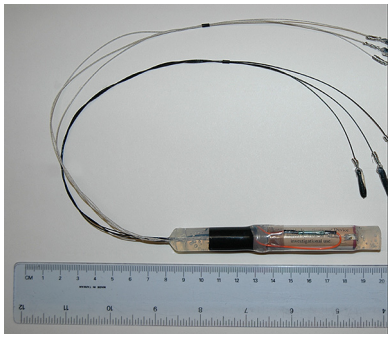

Figure 1. Human oscillating field stimulator.

a naturally occurring SCI from herniated thoracolumbar disks. Many dogs, especially dachshund, basset, and beagle breeds, are susceptible to explosive disk herniation and develop a rapidly progressing complete SCI (9). This complete SCI has been systematically studied in the veterinary literature and is termed a Hansen type I lesion (9). The prognosis for this injury is poor despite veterinary neurosurgeons giving emergent intravenous methylprednisolone and performing emergent imaging and surgery (10). The surgery is a laminectomy and diskectomy performed exactly the way human surgery is performed. Of dogs with Hansen type I lesions, 60% remain completely paraplegic, and 25% recover variable locomotion. Two prospective randomized controlled trials comparing the use of an implanted extraspinal oscillating field stimulator (OFS) plus steroids and surgery with a sham OFS plus steroids and surgery in dogs with Hansen type I lesions were performed at the Purdue School of Veterinary Medicine (6, 7). The OFS was left in for 14 weeks and then explanted and studied. The animals were analyzed at many time points. Both trials documented statistically significant greater neurologic recovery in the OFS group with no morbidity compared with the control dogs. The OFS device was durable and safe. In all of the aforementioned studies, it was learned that the treatment must be started within 18 days of injury to achieve neurologic recovery. Based on the scientific investigations, a human OFS device was manufactured at Purdue University, tested, and ultimately given U.S. Food and Drug Administration investigational device approval.

METHODS

OFS Device

The outside case of the OFS is made of a fluoropolymer and silicone sealant that have both been used in other human applications (Figure 1). The power block, timing/switching block, current regulation block, and failsafe device are inside the case. The electronic schematic and details of fabrication and operation of the human use OFS have been reported previously (6). Briefly, the power block provides the DC power source for the unit using a single 3.6-V organic lithium battery with a rated capacity of 2400 mA/H. The timing/switching block consists of a complementary metal oxide semiconductor 14-stage binary ripple counter device with an onboard oscillator timed for 15-minute intervals along with a single pole double throw analog switch. A failsafe semiconductor chip is programmed to shut the OFS down if the power decreases to 2.6 V, if there is a failure to oscillate, or if current changes indicate an internal short circuit. Current regulation is set by another semiconductor device that delivers 200 μA to each pair of electrodes for a total current of 600 μA. The electrodes are made of standard pacemaker cable and a platinum and iridium tip with a surface area of 4.72 mm^3. One set of three electrodes has black wires, and the other set has white wires. A magnet-controlled reed switch is used to turn the device on or off. When a magnet is on the switch, the device is turned off. When the unit is turned on, it delivers a field of 500–600 μV/mm and a current density of 42.4 $\mu A/mm^2$ for each electrode.

Human Trial

Entry Criteria. A phase I study was conducted on 10 human patients with complete SCI, and the results were reported in 2005 (25). Entry criteria for the study were very strict. All study patients had to be 18–65 years old. All had to have an acute complete SCI between the levels of C5 and T10 that remained complete for at least 48 hours before entry into the study. Penetrating injuries secondary to gunshot wounds or other devices were not allowed. To be eligible for the trial, all study patients had to be treated with intravenous methylprednisolone according to the National Acute Spinal Cord Injury Study (NASCIS) III protocol (8). All patients had to undergo imaging with computed tomography scan and magnetic resonance imaging. Complete spinal cord transection as evidenced by magnetic resonance imaging precluded entry into the study. Any spinal cord compression or spinal instability needed to be treated surgically before study eligibility (i.e., the OFS was not implanted at the same time as the decompression or stabilization procedure). The patient's SCI needed to remain complete after the decompression or stabilization procedure. The patient underwent somatosensory evoked potential (SSEP) monitoring after any treatment and had to have no conduction through the injury site. The patient had to be implanted within 18 days of injury. On study entry, a visual analog scale (VAS) score for pain and American Spinal Cord Injury motor/sensory score were obtained. The OFS device making pain worse was a major concern of the Food and Drug Administration.

OFS Placement. In the operating room, the anesthetized patient was positioned in the prone position. All cervical and high thoracic injuries were placed in three-point head fixation. Prophylactic antibiotics were given in all 10 patients. A midline incision was marked using fluoroscopic guidance to allow exposure of the injury level and one laminar segment above and below the injury. A standard exposure of the desired spinous processes, lamina, and facets was obtained in all 10 patients. The sterile OFS package was opened on the field, and the magnet was removed from the switch to turn on the device. Each set of electrodes of the OFS device were checked using an ampere/volt meter for accuracy of function and oscillation. After verification, a subfascial pocket for the stimulator was easily created in the caudal paraspinous musculature to minimize pain and discomfort. Three white electrodes were placed one segment above the injury, and three black electrodes were placed one segment below. For example, a burst fracture at C6 would have electrodes placed at C5 and C7, whereas a fracture-dislocation at T4-T5 would have electrodes placed at T3 and T6. One electrode was sutured to the spinous process using a nonabsorbable suture, and