Andara LifeScience, Inc.

Oscillating Field Stimulator (OFS)
Physician Manual

Table of Contents

Purpose

This manual describes the Andara Oscillating Field Stimulator™ (OFS) device and presents instructions for its use.

OFS Package Contents

One unit of the OFS device
One copy of the Physician Manual

For Questions

If you have questions regarding the OFS device, please call Andara's [1]toll-free number at 877-8ANDARA (877-826-3272).

Glossary

OFS	Oscillating Field Stimulator
SCI	Spinal-cord injury
MRI	Magnetic Resonance Imaging
CAT	Computerized Axial Tomography

Indication for Use

The Oscillating Field Stimulator (OFS) device is indicated for the treatment of spinal-cord injuries (SCI) of animals. It is designed to reduce the formation of scar-forming cells at the injury site and to produce behavioral recovery from the spinal-cord injury through regeneration of spinal cord nerve processes.

Description

The OFS device consists of a generator (power source and electronic circuit) sealed in clear, inert, medical-grade Teflon® and three pairs of insulated leads ending in uninsulated electrodes (Figure 1).

[1] Teflon® is a registered trademark of the Dupont company.

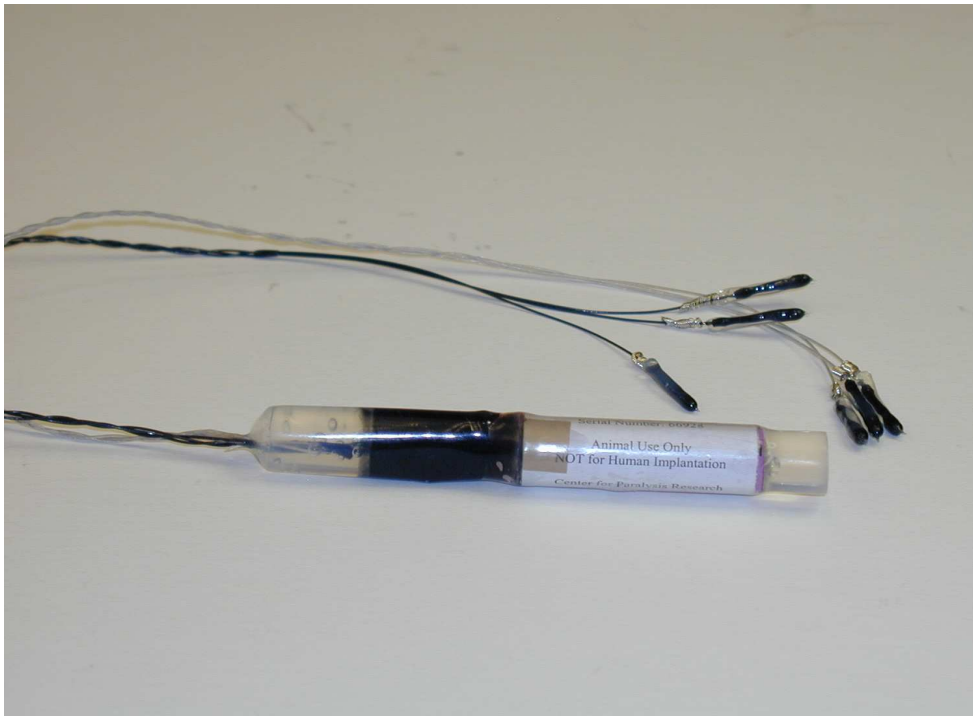

Figure 1 – The OFS Device for Animal Use Only

The generator produces a total of 200 μA of current from each of the three pairs of electrodes, totaling 600 A of current. This is associated with an electrical field of 300-500 μV/mm over the damaged region of spinal cord whose polarity is reversed every 15 minutes (Figure 2).

The four components of the OFS device that come into contact with body tissue and blood during implantation are:

1. The casing that encloses and seals the electronic components, which is a 0.02-inch thick sheet of fluorinated ethylene propylene (FEP, trade name Teflon®) extruded as a cylinder.

2. The surface of the electrode leads. The lead wires are commercially available pacemaker cable insulated with polytetrafluoethylene (PTFE).

3. The Nusil MED-1137 RTV silicone-based medical-grade elastomer sealing the ends of the Teflon® cylinder. This pressure-injected silicone prevents moisture from penetrating the OFS device's internal components.

4. The uninsulated platinum-iridium electrodes (medical-grade 90% platinum, 10% iridium annealed alloy wire) are free of mercury contaminants, with other trace metals occurring in the alloy in concentrations below 100 ppm.

Contraindications

There are no known contraindications to the use of this device.

Safety Precautions

The OFS device was designed to be used for all cases of paralysis in dogs resulting from spinal-cord injury. The OFS device can be used for (1) paraplegia secondary to fracture dislocation of the vertebral column (such as occurs with vehicle impact) and (2) intervertebral disc herniation (common in certain breeds such as the Dachshund).

There are no special safety considerations for the OFS device itself except those commonly associated with surgery under general anesthesia and with the overall state of health of the animal prior to and after spinal trauma. For example, the animal must be able to undergo surgery to manage the injury by conventional means. Pre-existing medical conditions (such as heart problems) should be considered by the surgeon.

1. Electrosurgery

Electrosurgical instruments are capable of producing radio-frequency voltages of such magnitude that direct coupling can occur between the cautery tip and lead system of the generator. To preclude the possibilities of burning tissues adjacent to the electrode or damaging the generator electronics, electrosurgical equipment should **NOT** be used on the patient after installation of the generator.

2. Diathermy

Therapeutic diathermy should **NOT** be used in the treatment of a patient who has an OFS device implanted since this equipment can also produce voltages that may damage the electronics. Diathermy **MUST NEVER** be applied over the site of any OFS device since the high currents induced in the lead may cause burning of the tissues in contact with the electrode tip.

3. Handling

The energy source and electronics of the generator are well protected within the generator case and will be unaffected by normal handling. However, the possibility of damage by mechanical shock, such as that of a drop onto a hard floor, cannot be precluded. Any device subject to this type of accident should not be implanted.

Explanted OFS devices should be disposed of in accordance with acceptable environmental standards and procedures. **DO NOT** dispose of any unit in an open fire.

Warning

MRI (Magnetic Resonance Imaging)

Animals should **NOT** undergo MRI while the device is implanted inside them.

Conventional Radiology

Conventional radiology, including computerized axial tomography (CAT), will not affect the functioning of the device and can be safely carried out after implantation.

Adverse Events

In two clinical studies involving 58 animal subjects treated up to 6 months, no adverse events or complications relating to the OFS device or to the application of the device were noted.

Clinical Trials

Two clinical trials support the indication and usage of the OFS device for the treatment of spinal-cord injuries in animals.

Study A – This study showed that an applied electric field in which the polarity is reversed every 15 minutes can improve the outcome from severe, acute spinal-cord injuries in dogs. The recovery of paraplegic dogs treated with an oscillating electric field (OFS) (approximately 500 to 600 µV/mm; n=20) was compared with that of sham-treated animals (n=14). Active and sham stimulators were coded, randomized, sterilized, and blinded for surgical implantation. The stimulators were of a previously unpublished design and met the requirements for Phase 1 human clinical testing. All dogs were treated within 18 days of the onset of paraplegia.

During the experimental applications, all received the highest standard of conventional management, including surgical decompression, spinal stabilization (when required), and acute administration of methylprednisolone sodium succinate. A radiological and neurological examination was performed on every dog entering the study, the latter consisting of standard reflex testing, urologic tests, urodynamic testing, tests for deep and superficial pain appreciation, proprioceptive placing of the hind limbs, ambulation, and evoked potential testing.

Dogs were evaluated before and after surgery and at 6 weeks and 6 months after surgery. A greater portion of experimentally treated dogs than sham-treated animals showed improvement in every category of functional evaluation at both the 6-week and 6-month recheck, with no reverse trend. Statistical significance was not reached in comparisons of some individual categories of functional evaluation between sham-treated and OFS-treated dogs (ambulation, proprioceptive placing); an early trend towards significance was shown in others (deep pain), and significance was reached in evaluations of superficial pain appreciation. An average of all individual scores for all categories of blinded behavioral evaluation (combined neurologic score) was used to compare group outcomes. At the 6-month recheck period, the combined neurologic score of OFS-treated dogs was significantly better than that of control dogs ($p=0.047$; Mann-Whitney, two-tailed). R. B. Borgens, et. al. “An Imposed Oscillating Electrical Field Improves the Recovery of Function in Neurologically Complete Paraplegic Dogs,” *Journal of Neurotrauma*, Volume 16, Number 7, 1999, pages 639-657.

Study B – A clinical trial of applied, slowly oscillating, weak electric fields was performed in dogs with naturally occurring spinal-cord injuries due to intervertebral disc herniation. Criteria for admission to the study were: complete paraplegia, defined by neurological exam and electrophysical testing; intact segmental reflexes; radiologic and myelographic evidence of spinal-cord compression due to disc herniation and a focal lesion, without appreciable rostrocaudal spread of necrosis; weight less that 16kg; onset

of paralysis less than 1 month before surgery. The injured cord was exposed by laminectomy, and decompressed by aspiration of disc material.

Active (n=13) and sham (n=11) stimulators were implanted subcutaneously, with platinum/iridium electrodes sutured to muscle several millimeters above the cord surface, at either end of the laminectomy site. Active stimulators delivered an estimated electric field strength of 135 - 210 µV/mm, switching polarity every 15 minutes, for 3, 6, and 15 weeks. Neurological and electrophysiological examinations were repeated approximately 6 weeks and 6 months after implantation.

Few complications were noted. None were attributable to current application. The group of dogs with active stimulators showed greater progress than the group of sham implants, with a trend towards greater recovery in all neurological measures, and evoked potentials. The difference in the combined neurological score between actively treated and sham-treated groups was statistically significant at 6 weeks (p=0.033) and at 6 months (p=0.036, Mann-Whitney *U*-test). R.B. Borgens, et. al., “Effects of Applied Electric Fields on Clinical Cases of Complete Paraplegia in Dogs,” *Restorative Neurology and Neuroscience*, 5 (1993), pages 305 -322.

Storage

The OFS package should be stored at room temperature (20-23℃/68-73℉).

Shelf Life

The expiration date is located on the storage package. The shelf life of the device is 12 months.

Sterilization

OFS devices are ethylene oxide sterilized that has been approved by FDA for human-use sterilization. Sterilization data appears on the inner pack. The sterile packaging is conventional medical-grade with a clear covering so the items inside the package can be plainly seen. A color-indicator strip, visible in the inner package, indicates exposure to ethylene oxide gas. The storage package should be inspected before usage to be sure that the seal has not been broken. Re-sterilization, if necessary, should be carried out using normal ethylene oxide procedures, but NOT in excess of 50ºC (122ºF). After re-sterilization, allow 72 hours for aeration in a warm (37ºC, 99ºF) ventilated environment.

Instructions for Use

The OFS device is indicated in the treatment of spinal-cord injuries for animals. Use of this device and consequential therapy are known to produce nerve regeneration for limited distances across and through the spinal injury, reduce the density of scar-forming cells at the injury site, and produce a behavioral recovery from both standardized transection injuries and compression injuries to the spinal cord in adult laboratory guinea pigs.

The OFS device is designed to be implanted at the time of **acute** – usually emergency – conventional surgical management (Decompressive Surgery/ Diskectomy) of the spinal-cord injury. In cases where this cannot or is not performed, the device can be surgically

implanted within three (3) weeks of the injury. The device is designed to be removed 14-16 weeks after the implantation surgery.

The following procedures should be performed only by a veterinary small-animal surgeon trained in the conventional, standard-of-care, surgical management of spinal injuries in dogs. For this reason, conventional discussion of typical surgical procedures including those involved in closing the surgical site and aftercare are not described here.

There are no known drug interactions with the OFS device; therefore, pain medications, antibiotics, and other appropriate medications as deemed necessary by the physician can be given to the patient. Methylprednisolone Sodium Succinate can be administered prior to or at the time of surgery, if deemed necessary by the physician.

Generator (Body) of the OFS device

The cylindrical generator or body of the OFS device can be placed subcutaneously in larger dogs or can be inserted into a “pocket” fashioned with a finger or blunt probe beneath the fat pad or between the fascial connections of muscle layers of the back beneath the back skin. The only consideration is that if the more superficial (subcutaneous) placement “stretches” skin tightly across/over the device in some (usually small) breeds, thus contact necrosis may occur over the 14 weeks of implant time. The surgeon can, if concerned, opt for a deeper placement of the generator at the time of implantation. This can also be done after the original implantation if superficial problems with skin stretched over the device become apparent.

Leads and Electrodes

The terminal of each lead has a black tab near the uninsulated metal electrode, providing a site for suture to muscle. All six of the electrode terminals are fastened to superficial paravertebral musculature of the spine by tethering with suture. **The electrodes *are not placed* within the bony spinal column, or the parenchyma of the cord. The former would interfere with the orthopedic management of the injury or spinal fusion, perhaps destabilizing the column in some cases. The latter would produce more, and unacceptable, injury to the spinal-cord soft tissue.**

Electrode Placement

The six OFS leads and electrodes are coded at the factory. There are three leads coded with black insulation and three leads coded with white insulation. All three of one set (*all* black or *all* white) are sutured to a vertebral segment rostral (head side) of the spinal-cord injury, and the other three electrodes to the “tail side” (caudal) to the injury. Since the polarity and the direction of the current reverses every 15 minutes, it does not matter whether black- or white-coded electrodes are placed rostral or caudal of the injury, only that three electrodes *of the same type* (black or white) are so placed, as pictured below (Figure 2).

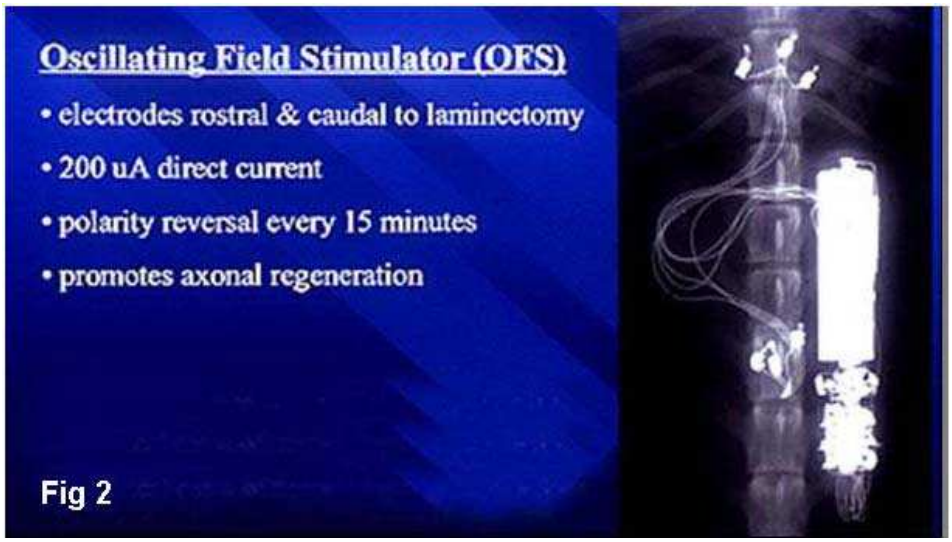

Figure 2 – OFS

Two of the three pairs of electrodes are sutured to the sides of the spine. At each rostral or caudal position, one electrode is sutured onto the musculature of each of the left and right lateral facets of the exposed vertebral segment. The remaining electrode of the cluster is sutured to the musculature of the dorsal (posterior) facet.

There are two suggested ways to determine at which vertebra, rostral or caudal, of the injury site to locate these electrodes. Radiology and/or myelography should be used to accurately determine the vertebral level of injury.

If the surgeon chooses to perform a durotomy at the site of injury subsequent to a lateral or dorsal hemilaminectomy, then the electrodes should be fastened at the rostral and caudal vertebral level *nearest the lesion* where healthy and undamaged spinal-cord tissue is revealed.

If a durotomy is not performed, then the electrodes should be fastened approximately 1 1/2 to 2 vertebral segments rostral and caudal to the injury site.

Surgical Implantation of the OFS Device in Canine Paraplegics

Preparation: OFS implantation is performed during conventional surgical management of spinal cord injury in the canine. These traumatic injuries are secondary to intervertebral disc herniation or fracture /dislocation of the spine. Both types of trauma can be treated with OFS. Prior to Surgery conventional “standard of care management” assumes that the damaged region of the spinal cord has been precisely located using radiology, preferably lumbar myelography. It is also assumed that conventional and appropriate anesthesiology, and surgical aftercare are followed.

General Surgery: The site of injury is surgically exposed by hemilaminectomy procedures on the same side (ipsilateral) to a lateralized lesion – or left

hemilaminectomy for ventral lesions. The longitudinal extent of the decompressive surgery at the injury site can usually be determined by radiographic methods prior to surgery, and can be confirmed and extended by surgical exploration. The length of area where bone is removed should continue until epidural fat and grossly normal spinal cord are visualized at both the rostral and caudal margins of the lesion. This surgical site is lavaged with cold sterile saline intermittently during the entire procedure described. Homeostasis can be achieved by various procedures (electrocautery, bone wax, application of gelatin sponge to control bleeding from the ventral venous sinuses, etc.), as this will not interfere with OFS therapy.

Surgical telescopes should be used for deeper exploration of the lesion and the removal of compressed disc material. The use of conventional spinal fixation devices in cases of fracture / dislocation will also not interfere with OFS therapy. Durotomy (using a # 12 blade) is suggested to determine the existence and/or extent of ascending / descending Myelomalacia.

Severe malacia extending more than one vertebral segment in longitudinal extent should disqualify the dog for OFS therapy. An autogenous fat graft is suggested as a covering for the exposed spinal cord to reduce postoperative fibrosis.

Implantation

Blunt dissection using probes or the surgeon's finger is employed to produce a pocket in the para-vertebral musculature – superficial to the spine and beneath the skin. This pocket need only be large enough to entirely accept the electronics package of the OFS device. One cluster of three electrodes is insulated with black Teflon, the other cluster with white Teflon. Each cluster of three electrodes is loosely sutured to lumbodorsal fascia. They are then routed through muscle layers to their respective locations above and below the injury, to be attached to the outside of the vertebral column. Redundant lengths of electrode wire is coiled loosely and attached to lumbodorsal fascia with suture. The black and white electrodes are routed rostral and caudal of the hemilaminectomy site. It does not matter which cluster is positioned rostral or caudal to the surgical site – only that all thee black and all three white electrodes are placed together in the same location. Said another way, black and white electrodes CANNOT be mixed together rostral or caudal of the lesion. Polypropylene suture is used to secure the individual uninsulated ends of each electrode (exposed platinum iridium coils) to the following three locations – Rostral and Caudal to the hemilaminectomy.

1. The musculature of the left articular facet
2. The musculature of the right articular facet
3. Within a small tunnel created in the bone of the base of the dorsal articular process.

The distance between the electrodes clusters, measured between the electrodes attached to the dorsal articular process varies with the size of the dog. Generally this distance is between 5 to 10 mm.

Surgical wounds are closed in layers by conventional techniques. The OFS device can be surgically removed 14 – 16 weeks after implantation.

Explantation of the OFS device

Explanting the OFS device requires general anesthesia. The generator or body of the OFS device is exposed and loosened from the implantation site. The electrodes are followed to their respective suture sites and removed, and the complete OFS device (generator, leads and electrodes) is withdrawn. The surgical wounds can be closed and aftercare post-surgery can all be handled in conventional manner.

Note: The OFS device should **not** be reused.

Conditions of Sale

The decision to implant an OFS device is purely a medical one determined in light of the special circumstances of each case. The manufacturer takes every care in the selection of components and in all steps of manufacture, quality control, and packaging.

The prescription and implantation of an OFS device are beyond the control of the manufacturer. Andara makes no claim that adverse reactions or medical complications will not result from the implantation, regardless of method of surgical implantation or method of use.

Andara, as the manufacturer of this device, does not practice medicine and does not recommend this or any other surgical technique for use on a specific patient. The surgeon who performs the implant procedure is responsible for determining and utilizing the proper techniques in each patient.

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

Replacement Credit Policy

In the event of a product failure due to manufacturing defect and/or failure of the product to perform according to specifications, a replacement will be provided only when all the following conditions are met:

1. The original device was implanted prior to the “Use Before” date indicated on the package, and
2. The explanted generator was returned to Andara within thirty (30) days of removal from the patient, together with a written report detailing the circumstances of its removal.

Return Goods Policy

1. Customers receiving damaged product may return the product for full credit.
2. Unopened, unexpired product in the original packaging may be returned if returned ninety (90) days prior to expiration. A full credit less a fee charged for restocking will be given to the customer.

3. Opened product cannot be returned for credit.
4. Outdated or expired product cannot be returned for credit.

Disclaimer

Andara Life Science, Inc. warrants that it exercises reasonable care in the manufacture of its products and that the products are free from defects in materials and workmanship under normal use and service. There is no expressed or implied warranty, including any implied warranty of merchantability or fitness for a particular purpose, on the Oscillating Field Stimulator product described in this publication. Under no circumstances shall Andara be responsible for medical expenses or any direct, incidental, or consequential damages, other than as expressly provided by law, arising from the purchase, use, removal, or replacement of the product(s) described in this publication. No person has the authority to bind Andara Life Science to any representation or warranty except as specifically set forth herein.

Description or specifications in Andara Life Science's printed matter, including this publication, are meant solely to generally describe the product at the time of manufacture and do not constitute any express warranties.

Andara Life Science will not be responsible for any direct, incidental, or consequential damages resulting from reuse the OFS device.