Photograph by Joe Raedle

Spinal cord stimulation
for injured soldiers with complex regional pain syndrome

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Spinal cord stimulation (SCS) therapy enhances pain relief over a long-term period, decreases the need for opioid analgesics, improves quality of life, increases the rate of return to work, and manages pain economically. These benefits make SCS therapy a viable treatment option for seriously injured soldiers with complex regional pain syndrome (CRPS).

Understanding CRPS

The United States has recently been faced with an increasing demand for medical-related services to treat the ever-rising number of soldiers wounded in combat. Approximately 21,000, or roughly 2% of deployed military personnel, have been wounded since the start of the wars in Afghanistan and Iraq.[1]

Sixty-five percent of combat injures account for wounds from improvised explosive devices, land mines, and shrapnel.[1] Some of those wounds are peripheral nerve injuries that lead to a number of different pain syndromes. In a case study of soldiers who fought in Operation Iraqi Freedom, the most common pain syndromes after blast injuries were CRPS Type II and phantom limb pain.[2]

In 1994, the International Association for the Study of Pain (IASP) renamed reflex sympathetic dystrophy (RSD) as CRPS Type I and the condition known as causalgia was renamed CRPS Type II.[3] According to the IASP, CRPS Type I has the following clinical findings: regional pain, abnormal sudomotor activity, skin color and sensory changes, abnormality of temperature, and edema. CRPS Type II has all the clinical findings of CRPS Type I, and also includes peripheral

nerve lesions.[4] Examples of the source of injury for CRPS I include scorpion stings and rib resections. Examples of the source of injury for CRPS Type II include motor vehicle crashes, and terrorist explosions.[3] CRPS refers to pain that can occur after extremities have been injured, lasting much longer and more severe than acute pain. Current treatments for pain syndromes consist of pharmacologic agents, nerve blocks, neuromodulation, physical therapy, psychological therapy, and surgical intervention for injured nerves.[5]

This article presents SCS as an effective treatment for patients with CRPS.

Incidence and prevalence

For hundreds of years, wars have caused trauma to the limbs of soldiers, many of which resulted in amputation. These injured soldiers continued to feel significant pain in one or more extremities for months or years after their wounds had healed. The most common of these types include neuralgia, phantom pain, and CRPS Type II.[6]

CRPS affects not only military personnel but also the general population. A study of CRPS Type I at the Mayo Clinic reports an incidence rate of CRPS Type I of 20.57 per 100,000 people. CRPS occurs more frequently in females than it does in males (4:1). CRPS prevalence peaks in midlife with the average age of onset at 46 years.[6]

In 2003, an approximation from a study by Sandroni et al.[7] suggests that more than 16,000 new CRPS Type I cases occur annually. Common causes of CRPS include a history of trauma, bone fractures, sprains, immobilization, and surgical procedures such as for carpal tunnel and invasive procedures such as venipuncture as well as I.M. injection.[8]

Etiology

To date, the pathophysiology of CRPS is not fully understood. However, de Mos et al.[9] propose that CRPS may involve five mechanisms: autonomic (sympathetic) nervous system dysfunction, somatic nervous system dysfunction, inflammation, hypoxia, and psychological factors.

Autonomic nervous system hyperactivity may result in increased sweating, trophic changes, and vasoconstriction of the affected limb. In the past, symptoms of sympathetically maintained pain (SMP) were considered symptoms of CRPS. A painful sensation from SMP results from sympathetic outflow through adrenergic responsiveness in target tissues. The treatment of SMP includes sympatholytic blocks; however, few CRPS patients benefit from this treatment.[8]

In somatic nervous dysfunction, continuous nociceptive input or nerve injury from CRPS can lead to spinal neural sensitization by lowering the stimulation threshold. This spinal neural sensitization may result in painful sensations instead of nonpainful sensations when a nonpainful stimulus is applied to an individual. In addition, spinal neural sensitization may result in an increased painful sensation, when an individual is responsive to normal painful stimuli.[8]

The inflammation mechanism is associated with lymphocytes, phagocytes, and mast cells that release classic proinflammatory cytokines, which include interleukin-1beta (IL-1beta), IL-6, and tumor necrosis factor alpha (TNF-alpha). IL-1beta and TNF-alpha together initiate persistent neuropathic pain, whereas IL-6 alone is able to sustain it.[10] In CRPS patients, levels of IL-1beta and TNF-alpha at affected sites occur mainly because nociceptive C-fibers are higher than those levels at unaffected sites. Increased levels of TNF receptor type 1 can trigger hyperalgesia in CRPS. Nevertheless, white blood cell count and C-reactive protein levels, which are indicators of inflammation, are normal in CRPS patients.[11]

Hypoxia results from extreme vasoconstriction that is affected by sympathetic nervous system dysfunction or a local imbalance between endothelial factors. Endothelial factors involve nitric oxide (NO), which causes vasorelaxation, and endothelin (ET-1), which causes vasoconstriction. In CRPS patients, NO levels are decreased while ET-1 levels are increased at the affected extremity.[11]

To date, because of a lack of high-quality studies, it is not known whether psychological factors may lead to CRPS. However, CRPS may result in psychological consequences such as the mode of anger expression. Anger-out means an expression of anger through verbal or physical methods because a painful sensation affects an extremity of the CRPS patient.[9]

Clinical symptoms of CRPS Type I

A noxious stimulus to an extremity usually results in CRPS Type I. CRPS Type I tends to affect upper extremities more than lower extremities. The location of symptoms may differ from the site of the injury on the extremity. Ninety-five percent of patients display their symptoms at sites that are not affected by the preceding injuries. In some studies, CRPS Type I affects the entire extremity versus the specific site of injury. In almost all case studies of CRPS Type I, injuries are associated with sensory, motor, autonomic symptoms, trophic changes, and psychological disturbances.[8] (See *Clinical features of CRPS Type I*.)

The pain sensitivity in CRPS patients is characterized by burning, throbbing, pressing, shooting, or aching. Before an onset of CRPS Type I occurs, pain is felt at the injury site. Continuous pain diffuses and spreads distally from the injury site, and swelling may develop distally from the injury site. The initial pain that is felt at the site of injury then disappears. Diffuse pain may disappear during the

onset of CRPS Type I, but reappear later in the course of the pain syndrome. Risk factors that trigger symptoms of CRPS Type I include physical load, painful stimuli, movement, and temperature changes. The swelling is often linked to the strength of stimuli. Abnormal sensation in CRPS Type I can be expressed in several ways. An individual with CRPS feels pain from innocuous stimuli (allodynia). For example, regarding allodynia, if an alcohol pad touches the painful area, the individual perceives it as being painful. An individual with CRPS has an increased sensitivity to pain, which may be caused by damage to nociceptors or peripheral nerves (hyperalgesia).[6]

Autonomic symptoms are common in CRPS. Blood flow to the skin is often abnormal and leads to vasomotor changes causing red, purple, and gray skin. This dark skin includes a thick outer layer of epidermis, which may peel on occasion. In cases with edema, CRPS patients display swelling of the distal part of the affected extremities. This edema may result from a blockage of the lymphatics that causes a persistent severe swelling of the extremity.

In clinical presentations of elevated skin temperature, CRPS patients develop an increase in skin temperature of about 2.5° C on the affected extremities compared with skin temperature on the unaffected extremities. Sudomotor dysfunction affects the sweat glands causing increased or decreased perspiration.[8]

In motor disturbance, 90% of CRPS patients show decreased muscular strength of the affected extremities without abnormality of tendon reflex. Clinical presentations of motor disturbance include tremors, weakness, muscular spasms, decreased range of motion, and dystonia.[8] Upper extremities are more often affected by motor symptoms than are lower extremities.[6]

More than 30% of CRPS patients develop trophic skin changes. These changes comprise disturbance in nail growth, increased or decreased hair growth, thinned glossy skin, joint stiffness, and hyperkeratosis. The thinned glossy skin may result from tissue atrophy.[6]

Most patients with CRPS develop symptoms of psychological disturbances. Anxiety, depression, fear, anger, and psychological symptoms are the derivatives of CRPS. The symptoms may worsen if these patients do not learn coping skills.[8] Fear of movement may increase inflammatory mediators and free radicals.[6]

Furthermore, patients with CRPS Type I can develop mirror-image pain. Mirror-image pain occurs in the unaffected side that is opposite to the affected side of the body. Mechanical allodynia usually results in mirror-image pain.[6]

CRPS Type I has three stages of clinical presentation. The first stage lasts 1 to 3 months and involves severe, burning pain in a localized area, localized edema, hyperesthesia, muscle spasms, rapid hair and nail growth, stiffness, and vasospasm that causes color and temperature changes. The second stage lasts 3 to 6 months and involves severe and diffuse pain, a wider region of edema, decreased hair growth, cracked and brittle nails, osteoporosis, and joint stiffness. The third stage involves intractable pain that may involve an entire extremity, irreversible trophic changes, muscular atrophy, severely restricted mobility, and severe osteoporosis.[12]

Clinical features of CRPS Type I[8]

Autonomic	Skin color changes Increase or decrease in sweating Edema Increase or decrease in skin temperature
Sensory	Allodynia Hyperalgesia Hyperesthesia Hyperpathia Hypoesthesia
Motor	Weakness Tremor Dystonia Myoclonus
Psychological	Suffering Fear Anxiety Anger Depression Inability to cope Behavioral disorders
Inflammatory/ trophic changes	Nail growth Hair growth Shiny skin Hyperkeratosis

Clinical symptoms of CRPS Type II

CRPS Type II is always associated with peripheral nerve lesions. Symptoms of CRPS Type II are less complex than symptoms of CRPS Type I, and the symptoms of CRPS Type II may not aggressively progress like the symptoms of CRPS Type I. Symptoms of pain, hyperalgesia, and allodynia in CRPS Type II patients affect the area of peripheral nerve damage, and these symptoms are less likely to spread far away from the injury location. CRPS Type II patients describe pain sensation as superficial and not deep inside the extremities.[6]

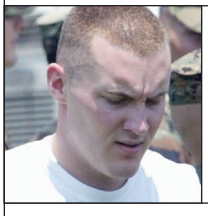
Treating patients with SCS therapy

SCS has been widely studied since 1967. Shealy et al.[13] initially developed SCS therapy to treat many types of nonmalignant pain. Based on the gate control theory of pain,

introduced by Melzack and Wall, SCS therapy proposes that stimulation of large afferent fibers can block pain signals at the dorsal horn columns.

In 2006, Stanton-Hicks[14] proposed that SCS is highly effective in the treatment of CRPS Types I and II by providing relief from pain, flow of blood (microcirculation) to the affected extremities, and cessation of tremor as well as mirrored effect. In addition, SCS successfully treats peripheral nerve injury and peripheral neuropathy.[15] The microcirculation can reduce the edema in patients with CRPS.[14]

A SCS therapy system consists of an implantable pulse generator connected to a lead wire which contains electrodes that deliver the impulse from the pulse generator to the spinal nerves. The practitioner inserts the lead wire into the epidural space, which lies between the anterior of the bony spinal canal and the outermost spinal cord membrane, the dura mater. The lead wire is connected to an extension wire that is tunneled under the skin to the pulse generator which is implanted under the skin, usually in the abdomen or buttocks. The electrodes receive the impulse from the pulse generator and deliver an electrical current, which creates a tingling sensation that interrupts the pain signals and leads to analgesic effects for the patient. The implantable device is programmed to allow control of voltage, pulse duration, pulse frequency, and function modes.



Ninety percent of CRPS patients show decreased muscular strength of the affected extremities.

Before placement of the implantable device, the patient undergoes a trial period with a temporary external device. During the procedure, the practitioner positions the lead wire in the epidural space and connects the lead wire to the external device for a trial period. If the patient improves and pain level diminishes in the trial period, the practitioner will implant an internal device.[14]

Non-rechargeable implantable devices require the battery to be replaced every 3 to 5 years.[15] The battery replacement time may vary based on the pulse frequency that is needed. A higher pulse frequency, which has been found to be successful in the treatment of CRPS, results in higher consumption of power by the battery in the implantable device. This necessitates replacing the implantable device earlier. A new option for SCS is a rechargeable implantable device. Rechargeability of the implantable device may result in a decreased need for replacing them.[16]

Complications of SCS include infection, abscess, subdural hemorrhage, and dural puncture which can occur during the placement of temporary and permanent SCS leads. Puncture of the dura mater causes cerebrospinal fluid leakage which results in severe headache that can be relieved by an epidural blood patch.[17]

SCS studies

In 2007, Verdolin et al.[3] demonstrated that patients with CRPS of 12 months duration, who are provided with SCS treatment, can decrease opioid usage, enhance quality of life and compliance with rehabilitation, and return to work as active duty military personnel. Verdolin conducted a retrospective study that described SCS treatment applied to 10 soldiers with CRPS of less than 12 months duration. All 10 patients had treatment for CRPS Types I and II at an interventional pain center. Eight of these patients were males whose mean age was 27 ± 7.4 years. Routine assessment included use of a numeric rating scale (NRS) for pain assessment and opioid doses calculated in morphine equivalents. Six of the 10 patients had been injured in Iraq or Afghanistan. After 6 months of SCS treatment, the NSR was reduced from 7.8 ± 1.3 to 1.6 ± 1.5 ($P < 0.0001$). Additionally, mean daily use of morphine was reduced from 103.5 ± 79 to 22 ± 15.8 mg ($P = 0.003$). All patients received physical therapy.[3]

In a prospective trial with 29 patients, Harke et al.[18] found that long-term SCS therapy helped 29 patients with CRPS Type I to enhance their pain relief, their functional status, and quality of life. Of the patients included in the trial, 16 patients reported upper extremity pain, 10 lower extremity pain, and 3 reported chest pain. Assessment consisted of a visual analog scale (VAS) ranging from 0 to 10 and functional status that assessed both upper and lower extremities. Upper extremities were assessed by a vigorimeter to test the strength of both hands at the same time. Lower extremities were assessed by the ability to walk without crutches. After SCS therapy, both pain and allodynia were diminished from 10 to 0-2 on VAS ($P < 0.01$). Ten of the 16 patients with CRPS in the upper extremities reported improvement on the vigorimeter. Eight of the 10 patients with CRPS in the lower extremities reported walking without crutches.[18]

In a longitudinal study, North et al.[19] concluded that patients with chronic, intractable pain, who had been treated with SCS over 2 decades, continued to report at least 50% relief from pain at 7-year follow-up. The researchers investigated how SCS treatments affected 205 patients with

chronic, intractable pain during the years 1971 to 1990. Mean age was 47.3 ± 12.0 years. Mean follow-up was 7.1 ± 4.5 years. The average duration of symptoms had been 11.8 ± 8.2 years. Fifty-four percent of these patients were male. Assessment included a 6-month follow-up and a mean 7-year follow-up. According to the follow-up, a success was considered a patient who reported at least 50% continued relief from pain. Concerning a decrease in pain sensitivity, at the follow-up, 52% of the 171 patients with SCS therapy achieved successful relief from pain ($P < 0.05$). Twenty-two percent of the 171 patients experienced unsuccessful relief from pain. Regarding return to work, patients under age 65 years received benefit from SCS therapy with improvement from 41% working preoperatively to 54% working postoperatively. Sixteen patients resumed full-time employment. Three patients returned to school full time. Five patients could work their part-time jobs. Finally, 15 patients advanced from part-time to full-time jobs.[19]

Kemler et al.[20] concluded that SCS therapy succeeds in pain reduction over the long term. After 2 years, SCS therapy would be cost-effective. The researchers carried out a randomized controlled trial (RCT) with a 5-year of follow-up to determine whether an SCS therapy can treat patients with CRPS Type I long term. Fifty-four patients were divided into two groups. Thirty-six patients were in an SCS and physical therapy group. Eighteen patients were in a physical therapy group. After 5 years, the mean of the VAS score decreased 2.5 cm in patients in the SCS and physical therapy group, whereas the mean of the VAS score decreased 1.0 cm in patients in the physical therapy group. The 36 patients in the SCS and physical therapy groups required 42 pulse generator replacements during 5 years of treatment, indicating a mean battery life of approximately 4 years per patient.[20]

The RCT for economic evaluation was conducted by Kemler and Furnée[21] in 2000 to 2001. In the study, 54 patients with CRPS Type I were divided into two groups that included SCS plus physical therapy group (36 patients) and physical therapy group (18 patients). The economic evaluation reported that a lifetime cost for SCS plus physical therapy is roughly $60,800 less than a lifetime cost with physical therapy alone. Kemler and his colleagues proposed that both SCS therapy and physical therapy were better than physical therapy alone and the lifetime cost of both SCS therapy and physical therapy was less expensive than physical therapy alone.[21]

Initiate therapy early

According to the various trials, achieving the full benefits of SCS occurs if SCS therapy is initiated early, not only to an injured soldier but also to any patient with CRPS. SCS has a demonstrated efficacy in treating patients with CRPS, and benefits include pain relief, decreased opioid usage, increased return to work, and enhanced quality of life.

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DOI-10.1097/01.NPR.0000383948.71724.11