Case Report

High Frequency Spinal Cord Stimulation for Complex Regional Pain Syndrome: A Case Report

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Complex regional pain syndrome (CRPS) is a chronic, debilitating, neuropathic pain condition which is often misdiagnosed, difficult to manage, and lacks proven methods for remission. Most available methods provide some relief to a small percentage of patients. Recent FDA approval and superiority of the Nevro Senza 10-kHz high frequency (HF10) spinal cord stimulation (SCS) therapy over traditional low-frequency spinal cord stimulation for treatment of chronic back and leg pain may provide a new interventional therapeutic option for patients suffering from CRPS. We provide a case report of a 53-year-old Caucasian woman who suffered with CRPS in the right knee and thigh for over 7 years. Implantation of the HF10 device provided over 75% relief of pain, erythema, heat, swelling, and tissue necrosis to the entire region within 1 month of treatment. Because the HP10 therapy provides pain relief without paresthesia typical of traditional low-frequency, this system may provide relief for patients suffering from chronic pain.

Key words: Complex regional pain syndrome, spinal cord stimulation, Nevro Senza HF10, erythema, knee, thigh

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Complex regional pain syndrome (CRPS) is a chronic pain condition characterized by spontaneous and evoked regional pain, usually beginning in a distal extremity, that is disproportionate in magnitude or duration to the typical course of pain after similar tissue trauma (1). CRPS differs from other chronic pain conditions with regard to the presence of pronounced inflammatory and autonomic changes in the pain-afflicted region. With varying severity, patients suffering from CRPS may exhibit hyperalgesia and allodynia; frank changes in skin color, temperature, and diaphoretic tendencies; edema and altered hair, skin, or nail growth to the affected area; reduced strength; tremors; and dystonia (2). Patients may present with further symptomology including altered body perception and proprioreception (3). CRPS may inflict significant impairments in a patient's ability to function and complete activities associated with daily living, which creates a huge burden to the patient and family (4).

CRPS affects an estimated 200,000 people per year in the United States, occurring approximately 3 to 4 times more often in women than men (5). The disease arises most frequently after injury, with fractures responsible for > 40% of cases. The underlying pathophysiology of CRPS involves a multifactorial process of both peripheral and central mechanisms (6,7). Possible factors involved in the development of CRPS include nerve injury, ischemic reperfusion injury or oxidative stress, central and peripheral sensitization, altered

sympathetic nervous system function or sympatho-afferent coupling, inflammatory and immune related factors, changes in the brain, as well as genetic, psychological, and disuse factors (8-20). Taken together it is clear to see that effective management of CRPS requires a wide variety of pharmacological (21), behavioral, and interventional strategies. In addition, a systematic review of clinical trials for the treatment of CRPS from 2000 to 2010 indicated that there was weak evidence for effective treatment of CRPS (22), emphasizing the need for more effective therapies for patients suffering with CRPS.

Bruehl's description of CRPS pathophysiology offers an explanation of the observed complex symptom and physical findings in this classic, albeit severe case of CRPS. Initiating injuries may be severe, but are often relatively minor and typically afflict an extremity. Genetics factors appear to play a role with higher prevalence of the disease noted in family members of patients with CRPS. Peripheral sensitization occurs with the release of neuropeptides (substance P, calcitonin gene-related peptide [CRGP] and bradykinin) at the injury site. A red, hot, edematous extremity is the result of plasma extravasation of neuropeptides and vasodilation. Bradykinin is thought to contribute to the release of proinflammatory cytokines such as TNF-a, as well as Interleukin-1B,-2,-6 from lymphocytes and mast cells. Proinflammatory cytokines are found in the fluid of skin blisters, plasma and cerebrospinal fluid. There is a decrease in nociceptive fibers in the afflicted region of the body with increased expression of adrenergic receptors. Sympathetic nervous system outflow of catecholamines may exacerbate symptoms related to nococeptive nerves developing adrenergic receptor expression. CRPS mediated central sensitization, mediated by the release of neuropeptides such as bradykinin and substance P, results in increased windup phenomenon in the cortical region supplying the affected limb. The associated somatosensory cortex of the brain demonstrates a decrease in size of the area representing the CRPS afflicted limb. There is expansion of the adjacent unaffected cortical regions into the somatosensory areas of the brain that have lost afferent input. Somatotrophic changes in the brain likely contribute to associated nondermatomal skin abnormalities resulting in the area afflicted being a regional rather than dermatomal distribution. CRPS pain and hyperalgesia demonstrate a significant correlation with degree of somatotrphic change (23).

Pain is commonly described as burning, constant and severe. The skin may demonstrate hard brawny edema (peau d' orange) with associated rashes, ulcers, and blisters sharply demarcated along a clear line. The symptoms may spread and become diffuse occurring in distant areas of the trunk, other extremities, or on the side of the face. Treatment involves addressing the psychosocial issues, medication management, physical / occupational therapy, as well as procedures such as sympathetic blocks and sympathectomy after successful sympathetic blocks. When conservative measures fail spinal cord stimulator therapy may be of benefit (24).

Case Report

The patient in question is a 53-year-old Caucasian woman with a professional career who has CRPS of her right knee and thigh. She previously had 4 arthroscopic surgeries on the right knee. The first surgery in April 1983 was performed related to a developmental defect which had resulted in a misaligned right patella. A second surgery was performed in April 2008 secondary to gradual worsening of right knee function, swelling, and fatigue. During her recovery from this surgery, the patient and her family were forced to evacuate emergently because Hurricane Gustav threatened New Orleans in August, 2008. During the evacuation, her vehicle was severely rear ended in a motor vehicle accident and her right knee was slammed into the car's dashboard area. At this point after the rear-end motor vehicle accident, the patient began to experience intense pain in the right knee with associated redness and swelling. Unfortunately, one week later she was misdiagnosed by an orthopedist with cellulitis for which she was unsuccessfully treated with antibiotics. The patient underwent a third right knee surgery in December, 2008. Nine months later in September 2009 she was finally diagnosed with CRPS by a neurologist. A final, fourth right knee surgery was performed in May, 2010, consisting of a partial medial meniscectomy, synovectomy, abrasion arthroplasty, chondroplasty, repeated repair of the anterior cruciate ligament, and excision of scarring throughout the knee capsule and severe synovitis. This fourth knee surgery successfully restored the biomechanics of the right knee; however, over time the CRPS migrated to include the entire right knee and thigh, and left and right shoulders and upper arms.

The patient's CRPS symptom complex began on the evening of the motor vehicle accident in August 2008. The severity of the patient's symptoms increased after the third and fourth knee surgeries. The patient described intense 8/10, constant, and unbearable deep

bone pain, as well as sharp and hot pain sensation to the associated muscle and skin. The right knee frequently erupted in painful and weeping blisters which were slow to respond to topical steroids or other topical treatment interventions. On examination, the knee appeared warm, with the anterior right thigh exhibiting a peau d'orange appearance. Erythema as well as multiple blisters and bullae in different stages of healing were evident across her right thigh. Additionally, the affected area continued to grow gradually over time, especially proximally, medially, and laterally. Also, pain and stiffness of the left and right shoulders and upper arms became increasingly evident.

The patient was prescribed an extensive list of medications owing to the variety of her symptomology, including but not limited to opiates (fentanyl, Butrans, oxycodone, Percocet, codeine), non-steroidal anti-inflammatory drugs (ibuprofen, naproxen), antidepressants (venlafaxine, paroxetine, aripiprazole), anticonvulsants (gabapentin, pregabalin), several different topical agents and lidocaine patches, hydrochlorothiazide for swelling, methylphenidate for fatigue, and stool softeners and laxatives for constipation. No analgesic provided her more than temporary, partial relief. Opioid analgesics were partially effective, but suboptimal doses were required since therapeutic doses rendered the patient overly sedated. The patient also relied on application of frozen gel packs to the affected areas throughout the day and an electric thermo-cooling circulating water wrap at night in order to cool the affected area. In addition to pharmacologic management, the patient received a single lumbar sympathetic block in 2013, which provided minimal relief for less than twelve hours. Physical therapy was unsuccessful and any standing, walking, or exercise induced swelling, increased pain, and heat at the affected region.

When evaluating the patient in the clinic, the patient offered a compelling history documenting the impact of CRPS upon her life in her own words:

"I suffer with excruciating pain, depression and fatigue. I often feel sad, anxious, overwhelmed, irritable, hopeless, helpless, and a complete loss of self. Simple daily tasks, such as walking, showering, and cooking dinner, are difficult due to the pain and minimal energy reserves. I suffer from severe stiffness, inflammation, redness, heat and swelling of the entire right knee and thigh. The affected area continues to enlarge distally, proximally, laterally, and medially. Because of the inflammation, the affected area is hot to the touch and I've relied on the use of research laboratory grade frozen gel packs for the past 7 years, 24 hours/day, 7-days/week. I also use an electric thermo-cooling circulating water wrap to sleep since the gel packs do not stay cold for 7 – 8 hours. As the CRPS has continued, it has had a greater impact on reducing my quality of life and interfering in my performing important roles as a professional, spouse, mother, and community member. I am unable to drive and walk even moderate distances. My ability to travel for business and pleasure has severely and negatively impacted my professional and personal life. My social life is minimal to nonexistent. Since starting the medications for CRPS my body weight has increased by 25 percent which contributes to low self-esteem and tremendous sadness. My pain experience is exhausting, exasperating and has had a negative impact on my family."

Initially the patient was averse to spinal cord stimulation (SCS). After nearly a decade of failed treatments, however, the decision was made to proceed with a SCS trial. The patient was offered a traditional SCS trial vs. high frequency SCS trial. Traditional SCS operates in a range of 2 to 1,200 Hz, with typical pulse frequencies of 40 to 60 Hz. High Frequency (HF) SCS delivers electrical stimulation pulses at 10,000 Hz for a short duration (30 μs). This novel method of stimulation does not rely on producing paresthesia, as does traditional SCS. The SENZA-RCT randomized control trial of 2015 demonstrated significant superiority of HF over traditional SCS, with 67% of HF patients experiencing pain relief at 12 months vs. 35% of traditional SCS patients (25). In light of this information, the patient opted for a trial of HF SCS.

After a successful HF trial of one week, a permanent implantation was performed 2 months later. The patient has been seen 4 times for follow-up evaluation since the procedure. She endorses marked pain relief, and no longer relies on any ice packs or cooling blankets being applied to the knee and thigh. The skin on the affected area has returned to a normal appearance. There are no weeping bullae, and the erythematous, peau d'orange appearance has completely resolved. The pain and stiffness of the shoulders and upper arms has also resolved. The patient enjoys a much more active and enthusiastic life without pain in the knee and thigh region. Within 4 months of the permanent HF SCS implant, the patient has discontinued use of all anticonvulsants and reduced opiates by 75%. It is anticipated that there will be a reduction in the use of the other pharmacological therapies used to treat the CRPS over the coming months.

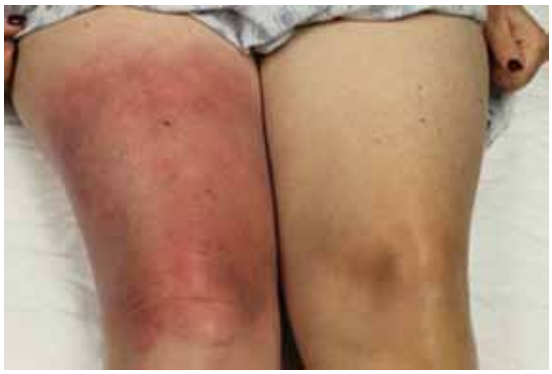

Fig. 1. *Before HF SCS. The right knee and thigh were hot to the touch, with the anterior right thigh exhibiting a peau d'orange appearance. Erythema as well as multiple blisters and bullae in different stages of healing were evident across her right thigh.*

Discussion

Chronic CRPS is a complex biopsychosocial condition which responds most often to integrated multidisciplinary treatment which includes psychological, medical, and physical and occupational therapies (26). Unfortunately, limited data exists describing the precise role of HF SCS in the treatment of CRPS. There have been no randomized control trials (RCTs) involving multidisciplinary care specifically for patients with CRPS.

Common drug treatments include initial trials with oral corticosteroids, anticonvulsants (e.g., gabapentin), analgesic antidepressants (e.g., duloxetine), transdermal lidocaine patches, and opioid analgesics. Gabapentin may somewhat alleviate pain in CRPS, according to one RCT, but opioid analgesics were not found to produce any significant analgesia in CRPS (27,28). No RCTs are available concerning antidepressants and lidocaine patches in CRPS.

A 2013 Cochrane review reported low quality evidence for pharmacologic treatment of CRPS with bisphosphonates, calcitonin, and subanesthetic intravenous ketamine (29). It also described low quality evidence for CRPS focused physical and occupational therapy, as well as low and medium quality evidence that local anesthetic sympathetic ganglion blockade and guanethidine intravenous regional blocks are ineffective.

After failure of the above approaches, many clinicians suggest a trial of SCS. SCS has demonstrated superiority over conventional medical management for many chronic pain conditions, including failed back surgery syndrome and CRPS (30). A RCT of SCS trials in CRPS found that two-thirds of patients successfully experienced significant analgesia (31). Permanent implantation is usually pursued following a successful trial, with an emphasis on functional improvement and normalization of activities of daily living.

Several studies have been conducted examining the efficacy of HF SCS in the treatment of chronic pain. A 2016 systematic review of SCS for chronic spinal pain confirmed the efficacy of all forms of SCS (low frequency, traditional, and HF) in the treatment of chronic back and leg pain (32). This same review reported significant improvements in pain relief in patients treated with HF SCS over traditional SCS, at 79% of patients treated with HF experiencing at least 50% reduction in pain score as compared to 51% of patients treated with traditional SCS experiencing at least 50% reduction in pain score. Of note, patients with leg pain performed even better under HF SCS treatment than those undergoing traditional SCS, with 67% responding compared to 43%, respectively. While not specifically examining patients with CRPS, this study nevertheless demonstrated the effectiveness of HF SCS.

Another prospective, multicenter study examined 82 patients with chronic, intractable pain of the low back and legs over a 24 month period (28). This study by Al-Kaisy et al found that 88% of patients experienced significant improvements in pain scores and elected to undergo permanent implantation. Of those, ninety percent attended a 24 month follow up visit, and endorsed a decreased in mean back pain from 8.4 ± 0.1 at baseline to 3.3 ± 0.3 ($P < 0.001$), and mean leg pain from 5.4 ± 0.4 to 2.3 ± 0.3 ($P < 0.001$). Along with pain relief, significant reductions in opioid use, Oswestry Disability Index scores, and sleep disturbances were reported. Again, although the study group in focus was not isolated to CRPS, the HF SCS has continued to demonstrate superiority over other treatment modalities for chronic pain of the low back and leg.

In retrospect, it is plausible that recovery from the second arthroscopic knee surgery combined with the sudden impact of the rear-end collision created the perfect storm for the onset of CRPS in this patient. Arthroscopic surgery is the most common inciting event in developing CRPS of the knee (33). Specific to the present case, while the reduction in knee pain and return

of functional status is remarkable, the authors would like to highlight the striking change in the objective appearance of the skin over a 12 x11 inch area on the patient's right thigh. Prior to HF SCS therapy, the heat and lesions consistently affecting the patient were one of the most problematic and disabling aspects of her illness (Fig. 1). The skin lesions continue to resolve post-permanent HF SCS implant, and the skin appearance is returning to normal, as evidenced by the photographic image of the knee and thigh 4 months post-permanent HF SCS implantation (Fig. 2).

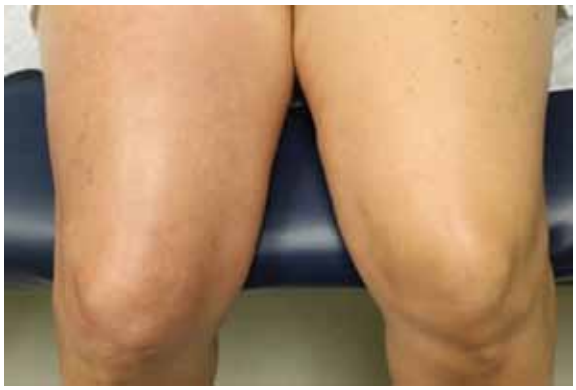

Fig. 2. *Four months after HF SCS. The signs and symptoms of CRPS have resolved.*

Conclusion

The role of neuromodulation in chronic pain conditions continues to evolve. SCS has proven to be an effective means of treating a variety of these conditions. As the devices and technology continue to evolve, added benefits are being revealed. The rapid, dramatic response of our patient's myriad of symptomology to HF SCS is promising. Further investigation into the mechanism of action of HF SCS in the treatment of CRPS is warranted in the future.

Disclaimer

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Conflict of interest

Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

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