CLINICAL REPORT

Scrambler Therapy® MC-5A for Complex Regional Pain Syndrome: Case Reports

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■ **Abstract**

Background: Complex regional pain syndrome (CRPS) is a disorder that is often challenging to treat and can be associated with a prolonged course of severe pain. Therapy of CRPS remains controversial; the pain often can be very difficult to control, and treatment includes medications, physical therapy, regional anesthesia, and neuromodulation.
Aim: We evaluated Scrambler Therapy® (ST) in terms of efficacy, safety, and durability of treatment effect in patients suffering from CRPS.
Materials and Methods: We report the response to ST in four patients with CRPS referred to the Pain Center of Bambino Gesù Children's Hospital. The patients previously did not respond to conventional and nonconventional medical treatments.
Results: The treatment with ST was found effective in all four of our patients; they obtained pain relief for long periods and an improvement in their quality of life. We observed a progressive improvement with complete disappearance of neuropathic pain. Patients also reported a muscle strength increase that allowed them to resume normal daily activities.
Discussion and Conclusion: We conclude that ST may offer a therapeutic opportunity for patients with neuropathic pain resulting from CRPS, without side effects and with minimal discomfort during treatment. The observed pain relief indicates that ST could be an effective option for such patients. ■

Key Words: complex regional pain syndrome, Scrambler Therapy, electrical pain stimulation, neuropathic pain, neuromodulation, nonconventional therapy, chronic pain, quality of life

INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic neuropathic pain that usually affects a single limb and typically follows an initiating noxious stimulus due to injury, surgery, stroke, or heart attack.[1–3] Studies found incidence rates of CRPS ranging from 5.46 (United States)[4] to 26.2 (The Netherlands)[5] per 100,000 person-years. Sandroni estimated the prevalence to be 20.57 per 100,000 person-years.[4] CRPS is more common in women, increasing with age,[4,5] and may follow a more severe course in younger people.[4]

The syndrome may develop in the setting of a documented nerve injury (CRPS type II) or in the absence of such damage (CRPS type I).[6,7] Despite this traditional distinction, signs, symptoms, and treatment of these two subtypes of CRPS are very similar. Diagnosis is clinical; Budapest's criteria have been updated and are widely accepted. Patients may

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experience sensory, vasomotor, and sudomotor abnormalities and motor–trophic changes in the affected extremity.[1,7–9] In most cases, significant functional impairments with disability and psychological distress are both present.[2,10]

There is no definitive medical treatment for patients with CRPS, and management is still a challenge. Because of the absence of effective medical treatments, invasive and expensive interventions, such as spinal cord stimulation and intrathecal drug delivery systems, are often used. The lack of adequate treatments for CRPS is the result of an incomplete understanding of its pathophysiology that involves inflammatory, vascular, sympathetic nervous system, cortical, and spinal mechanisms.[11]

Scrambler Therapy® (ST) derived from the development of a theory model, beginning in the mid-1980s;[12] the first clinical appearance in literature was dated 2003.[13] ST is an innovative device for pain treatment that attempts to relieve pain by providing "no pain" information via cutaneous nerves to block the effect of pain information. ST synthesizes 16 different types of nerve action potentials similar to endogenous ones, assembles them into sequences, and uses algorithms to determine a patient-specific cutaneous electrostimulation to reduce pain.[14] Marineo,[13] the ST developer, published the first study on the possible clinical application in 11 patients with refractory abdominal cancer pain. Subsequently, ST has relieved various forms of refractory chronic pain in several studies: neuropathic pain, including failed back surgery, brachial plexus neuropathy, and others;[15] refractory chemotherapy-induced peripheral neuropathy;[16–18] a wide spectrum of cancer-related pain;[19,20] back pain;[21,22] chronic neuropathic pain (spinal cord stenosis, failed back syndrome, postherpetic neuropathy);[14] postherpetic neuropathy;[23,24] and the main causes of chronic pain, including postherpetic neuralgia, chronic low back pain, polyneuropathy, peripheral neuropathy, and chronic pain due to other causes.[25] So, although there is some evidence for efficacy of ST in cancer neuropathic pain and in nonmalignant neurophatic pain conditions,[13–28] the evidence is sparse and scarce in CRPS.[28]

We report four adult patients with CRPS who had difficulty in pain control with conventional and nonconventional therapy, and refused invasive treatment, but benefited from ST in terms of efficacy and safety as well as durability of the treatment effect.

METHODS

All four patients had a clinical diagnosis of CRPS according to Budapest's criteria.[1] In view of their poor response to previous conventional pharmacotherapy and nonconventional treatments, and because they refused other invasive treatments, we proposed electroanalgesic treatment with ST.

With approval of the Institutional Ethics Board and informed consent, patients received ST at the Center for Pain Medicine at the Bambino Gesù Children's Hospital, where pediatric and adult outpatients are treated.

Each patient received a 45-minute daily treatment program for 10 consecutive days, but in view of the minimal risk and cost involved in ST, we elected to treat the patients with a more flexible treatment schedule. Nevertheless, ST was not performed if pain was not present, and the situation was reassessed the following day. Our standard protocol provides an average cycle of statistical processing of 10 applications. The cycle is stopped early if the patient has no pain as pain is the only symptom that guides the treatment. On the other hand, the number of applications can be increased if there is increasing pain relief after each treatment. The intensity of the electric stimulus that modulates and transmits the synthetic nonpain information varied from patient to patient. The pulse intensity was based on the maximum intensity perceived by each patient without any additional pain or discomfort. No additional fine-tuning was necessary as the rest of the treatment was fully automated by the simulation software.

We evaluated the degree of pain using the 0 to 10 numeric rating scale (NRS). We also recorded for each patient during each daily session of ST treatment (1) average pain in the previous 24 hours, (2) current pain, (3) pain during treatment, (4) pain after treatment, (5) pain interference with sleep, (6) pain interference with movement ability, and (7) pain interference with quality of life.

CASE REPORTS

Four patients, three female and one male, were referred to our Pain Center for severe intractable neuropathic pain:

1. A 58-year-old woman (Patient 1) with neuropathic pain located in her right upper arm that started 3 years ago, 2 months after a traumatic simple fracture of her radius and ulna.
2. A 70-year-old woman (Patient 2) affected by neuropathic pain located between the distal third

of the right thigh and ipsilateral ankle that developed after a lower right limb trauma (x-ray negative for fracture) 3 years before. She presented a right sciatic nerve injury caused by compression of post-traumatic hematoma and underwent surgery. Two months after discharge from hospital, she started to have pain as well as motor and sensory disturbances of her right lower limb.

3. A 68-year-old woman (Patient 3) with neuropathic pain of the left forearm, mostly at the wrist and extending to the fingertips. Her symptoms began 1 year earlier, 2 months after falling and having a fracture of her radius and ulna.
4. A 41-year-old man (Patient 4) developed neuropathic pain of his right hand and wrist. The pain was secondary to a fall wherein he hit the ventral part of his hand on the tarmac. X-ray was negative for fracture. The pain started 20 days after removal of the bandage and persisted for 4 months despite therapy.

The symptoms of our patients met Budapest criteria as well as the diagnosis of CRPS type I (Patients 1, 3, and 4) and CPRS type II (Patient 2) (Table 1). In fact, all four patients had continuous pain that was disproportionate to any inciting event, had at least one sign in two or more categories, had at least one symptom in three or more categories, and no other diagnosis could better explain the signs and symptoms. The main symptoms were weakness, allodynia, hyperalgesia, hyperesthesia/hypoesthesia, edema, vasomotor changes with increased sensitivity to cold and heat, temperature asymmetry, functional disability with lacked strength, dry and flaky skin with trophic changes, and frequent nocturnal awakenings due to pain (Table 1).

Prior to ST, our patients were treated with conventional pharmacological therapy and nonconventional treatments without any relief (Table 1). The pain score ranged from 7 to 10 on the NRS scale at the beginning of ST. The pain intensity diminished, and complete relief was obtained after 7 to 12 days in all of our patients. In addition, they noted a significant improvement of quality of life with complete functional recovery. They all returned to their usual daily activities and developed normal sleep patterns (Figure 1). Hypotonia of the right foot persisted in Patient 2. When followed up after 6 to 21 months, the patients did not need any medication and were free from pain (Table 1). Patient 2 had a 1-year relief of her pain, but returned for a mild pain in her right knee at the site of a scar. She was treated with local neural therapy and had complete disappearance of the pain.

DISCUSSION

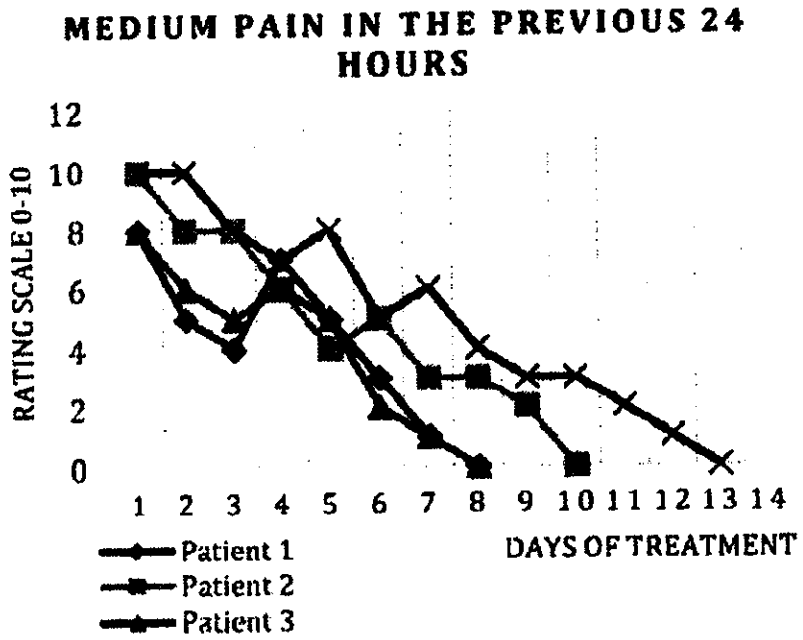
The successful relief of pain in our patients supports a possible therapeutic role of ST in subjects with CRPS. ST employs a multiprocessor device (Scrambler Therapy® MC-5A) to simulate the function of five specialized artificial neurons in constructing dynamic, synthetic nonpain information. The equivalent of the action potentials is generated by artificial neurons and transmitted to the skin by surface electrodes instead of endogenous pain information. The summary statement of "nonpain" is obtained by stimulating the C fiber surface receptors, selected through an appropriate time duration of the pulses in accordance with the principles

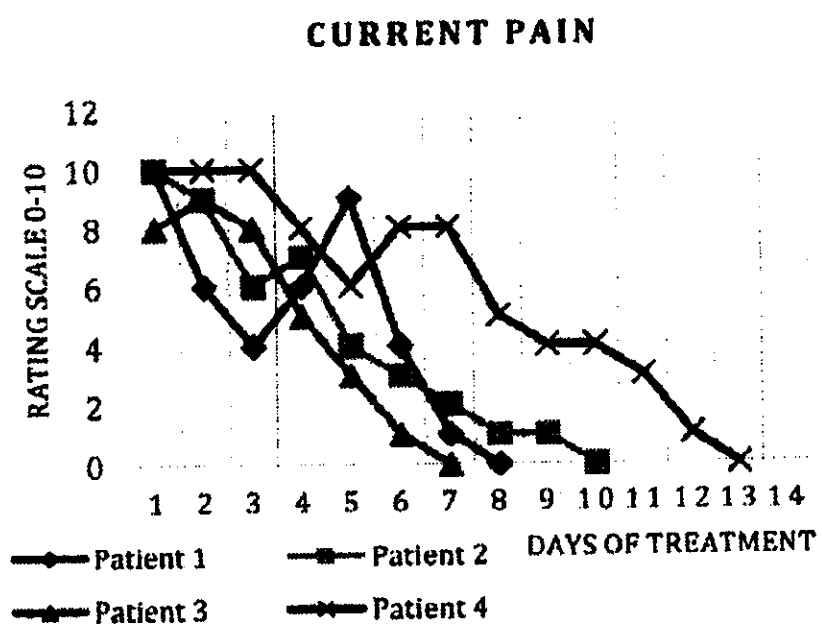
Table 1. Patient Characteristics and Outcomes

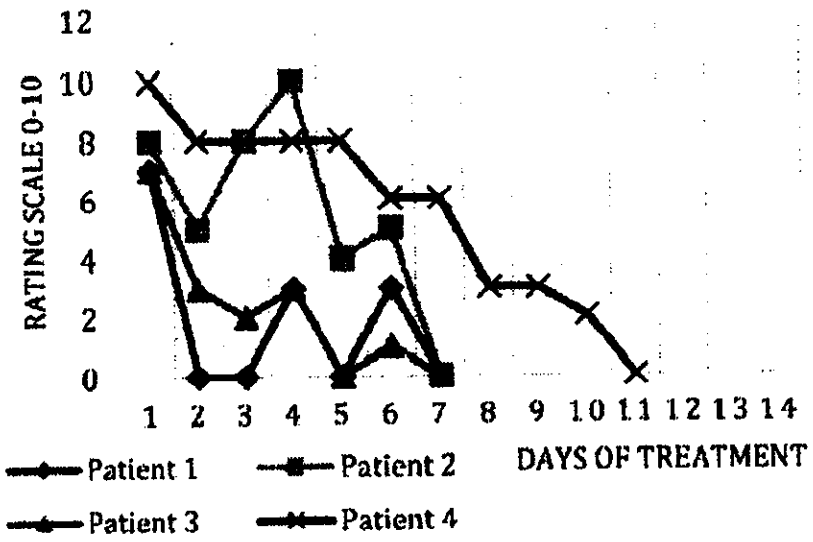
Patient	Age (Years)/Sex	Type of CRPS*	Affected Limb	Category of Signs/Symptoms	Duration (Months)	Treatments	NRS (0 to 10 Score)	Time for Relief of Pain (days)	Follow-Up (Months)
1	58/female	I	Right forearm	Sensory, vasomotor, edema, motor	38	NSAIDs, tramadol, physical therapy, acupuncture	8 to 10	7	6
2	70/female	II	Right thigh/ankle	Sensory, vasomotor, motor	36	NSAIDs, tramadol, gabapentin, pregabalin, physical therapy, TENS, magnetic laser therapy, neurolytic surgery	10	10	18
3	68/female	I	Left forearm	Sensory, vasomotor, motor, edema	12	NSAIDs, tramadol, physical therapy	7	7	21
4	41/male	I	Right hand/wrist	Sensory, edema motor/trophic	4	NSAIDs, gabapentin physical therapy	10	12	9

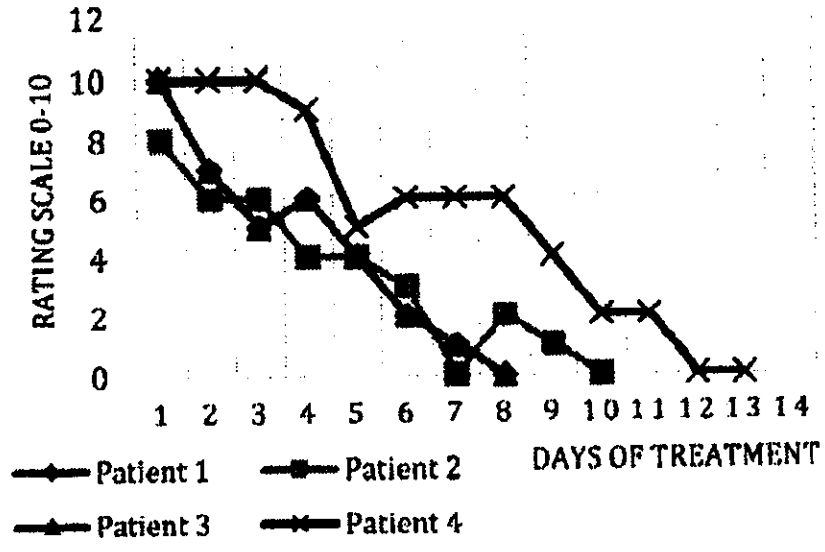
*All patients: continuing pain that is disproportionate to any inciting event.
CRPS, complex regional pain syndrome; NRS, numeric rating scale; NSAID, nonsteroidal anti-inflammatory drug; TENS, transcutaneous electrical nerve stimulation.

of chronaxie.[29,30] The treatment is applied using single-use silver gel surface electrodes, two for each channel, and 1 or more for independent channels (maximum 5) of the device, as needed. The procedure for ST starts with a clear identification of the pain area. The electrodes are not applied directly on the painful area, but placed on









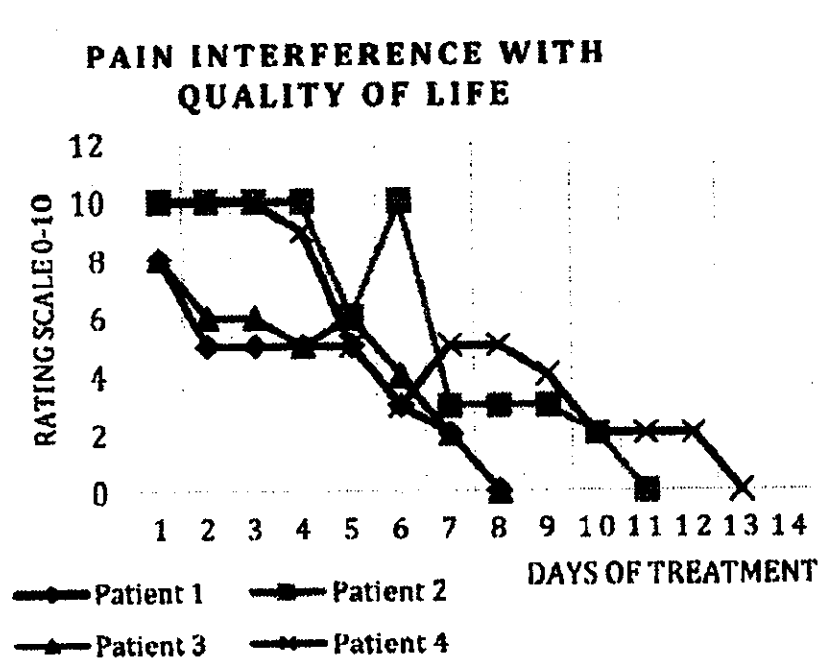


Figure 1. Response to Scrambler Therapy in the four patients considering single items.

the skin in the dermatome proximal and distant to the painful area. The positioning of the electrodes is the most critical part of the treatment; it is for this reason that it requires a specific training course. Basically, the operator is guided by the geometry of the area of pain. Once electrodes are placed, the analgesic efficacy can be verified by slowly raising the stimulation level, then deciding whether it is necessary to use other channels or change the stimulating area in order to obtain whole coverage. After every daily treatment, before starting the next one, it is necessary to evaluate the pain area again: the painful area can change and electrodes must be attached in a different way. After the placement of electrodes, electrical stimuli are applied. Intensity is gradually increased to the maximum value tolerated by the patient. This stimulus must not cause any additional pain or discomfort. In special cases, if pain involves the entire extremity, it is possible to place the electrodes even in the areas of pain. In this case, the positioning of the electrodes becomes empirical and greater experience of the professionals is required; in fact, it is necessary to seek areas to stimulate that do not cause discomfort or increased pain compared to the initial one.

We propose that ST can be considered in the treatment of patients with CRPS, especially those who have failed conventional and nonconventional treatments and before using invasive techniques. In fact, CRPS is a disorder that is often challenging to treat and can be associated with a prolonged course of severe pain. CRPS is characterized by chronicity and relapses that result in significant disability, poor quality of life, and other healthcare and societal costs.[8,31]

The main goals of CRPS treatment are to relieve pain, decrease morbidity, and return the patient to a more functional status.[31] Therapy for CRPS remains controversial and includes medications, physical therapy, regional anesthesia, neuromodulation with electrical stimulus (spinal cord stimulation and peripheral nerve stimulation), and transcutaneous electrical nerve stimulation (TENS). TENS and ST have one modality in common: noninvasive electrical stimulation. They are technically different and have different mechanisms of action. TENS is based on the gate control theory and is specifically designed to stimulate myelinated fibers and avoid the stimulation of C fibers. In contrast, ST specifically uses C fibers to relieve pain.[25]

Complex regional pain syndrome is a multifaceted syndrome. Comprising both central and peripheral pathophysiology, it frequently contain psychosocial components that represent additional pivotal diagnostic features.[3] Our patients had many unsuccessful experiences with pharmacological or other therapeutic options before ST. Treatment with ST was effective in all four of our patients; they obtained both pain relief (Table 1) and improved quality of life (Figure 1).

There was complete disappearance of pain and hyperalgesia/allodynia, as well as improved muscle strength and trophic changes with a return to normal activities in treated patients at follow-up. In addition, our patients' quality of life improved with regard to their daily activities and sleeping, similar to what was described in patients with chemotherapy-induced peripheral neuropathy.[17,18]

The response is similar or better than outcomes reported for spinal cord stimulation,[32,33] dorsal root ganglia stimulation,[34] or other neurostimulation therapies.[35]

Promising results have been reported with ST in the treatment of various forms of neuropathic pain, such as chemotherapy-induced peripheral neuropathy, postherpetic neuralgia, and postsurgical pain syndrome.[14–19,28] Only one study reported good results in patients with CRPS, but it did not report characteristics or follow-up.[28] ST should be tailored because each patient may require different numbers of sessions to reach the maximum positive effect and to maintain efficacy during follow-up. ST also proved to be an effective treatment method, with no side effects for patients suffering from various types of neuropathic pain.[14,16–20,23–25,28]

It is probably better for patients to be free from anticonvulsant medications during ST. This is because they have opposing mechanisms of action. In fact, an anticonvulsant may prevent the stimulus to progress along the nerve fibers. Anticonvulsants, especially in high dosage, may inhibit the effectiveness of ST due to their interference with the propagation of action potentials.[25] In our patients, nonsteroidal anti-inflammatory drugs, tramadol, and gabapentin doses were tapered during ST and finally stopped. These may be the reasons for the small number of ST sessions in Patients 1 and 3. Our patients refused other approaches, especially invasive, and preferred to experiment with ST because of its lack of side effects.

The presence of a neuropathic or mixed neuropathic–nociceptive pain condition could be associated with a positive ST treatment outcome. In fact, patients with a neuropathic pain condition were associated with a 25-fold higher response to ST than patients with nociceptive pain, and a mixed pain condition showed an 11-fold higher response rate than a nociceptive pain condition.[26]

Despite our small number of patients, a limitation of our report, we believe that our long-term results are encouraging and that ST is a potential novel treatment that may significantly improve chronic neuropathic pain due to CRPS. Patients unresponsive to previous conventional pharmacotherapy and nonconventional treatments are highly motivated to find an effective treatment. In addition, in our experience, patients agreed to try ST because they realized early the effectiveness and safety of the treatment.

CONCLUSION

ST, a novel noninvasive approach for pain control, may offer a therapeutic opportunity for patients with neuropathic pain resulting from CRPS, with no side effects and minimal discomfort during treatment. In our clinical experience, the pain relief obtained with ST indicates that this therapy could be a safe alternative for patients with neuropathic pain due to CRPS who have responded poorly to conventional treatment or who are afraid of undergoing invasive treatment. Therefore, validation of ST is necessary, and more patients with similar complaints need to be investigated. In terms of significant pain relief and improvement of quality of life, the results obtained in our patients should encourage further research with specific protocols and validated scales. New controlled studies should be performed to better assess and confirm the efficacy of ST as a first-line treatment for all chronic neuropathic pain, including CRPS.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1–S3. Pictures of Scrambler Therapy device.

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