

Spinal Cord Stimulation in Complex Regional Pain Syndrome Type I of Less Than 12-Month Duration

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Introduction: Complex regional pain syndrome type 1 (CRPS-1) has a 31% probability of becoming chronic. The early use of spinal cord stimulation (SCS) has been recommended as a strategy to prevent chronicity and functional impairment.

Methods: In a prospective study, we treated 74 CRPS-1 patients with a mean disease duration of 17 weeks with standard therapy consisting of physical therapy, topical dimethyl sulfoxide, analgesics, transcutaneous stimulation, and sympathetic blockade. Patients who did not respond to standard therapy were offered a treatment with SCS. In these patients, we investigated the impact on pain, quality of life, and function.

Results: Out of these 74 patients treated with standard therapy, six patients were included for early SCS treatment. The overall mean pain relief after one year was 35%. The mental component of the Short Form 36 improved; however, there was no effect on the physical component. None of the SCS treated patients showed a clear improvement in functional outcome.

Discussion: We conclude that the feasibility of performing a randomized controlled trial on early SCS therapy in CRPS-1 is low because of the good disease improvement with standard therapy in the first year after onset. This study raises questions about the need to use SCS early in the course of CRPS-1 because of the probable lack of additional benefit compared with SCS in chronic CRPS-1.

Keywords: Complex regional pain syndrome, functional restoration, neuropathic pain, prospective study, spinal cord stimulation

Conflict of Interest: All authors state no conflict of interest.

INTRODUCTION

Complex regional pain syndrome type 1 (CRPS-1) is a severe chronic pain condition characterized by sensory, autonomic, motor, and dystrophic signs and symptoms. It usually occurs after trauma and is characterized by spontaneous and evoked pain, which is disproportionate in severity and duration to the expected course of the initiating trauma (1). The reported incidence varies from 5.46 to 26.2 per 100,000 person years. Women are affected 3.4–4 times more often than men (2,3). In general, the outcome of chronic CRPS is not favorable. After one year, signs and symptoms in patients with CRPS are well developed and pain is refractory, with the majority of patients demonstrating only moderate increase in symptoms over the years (4). In a population-based cohort study of 102 CRPS patients, 31% remained incapable to work after two or more years (5). Of these patients, 64% still showed persistent signs and symptoms 5.8 years after onset of the syndrome (range 2.1–10.8 years). CRPS therefore is a serious condition with a high probability of chronicity and residual impairment. Recommendations from an expert panel suggest concomitant use of psychologic, rehabilitation, and interventional pain management techniques (6). Therapy aimed at restoring function should be started as soon as possible, as any delay in treatment is likely to worsen outcome. Spinal cord stimulation (SCS) is a more invasive technique to be considered when other treatments fail. A

systematic review reports SCS to be an (cost-) effective therapy in the management of patients with chronic CRPS-1 (7). However, despite its efficacy in the treatment of pain, SCS performed in chronic CRPS-1 showed no important improvement in functional outcome (8). Therefore, the early use of SCS (less than one year) for the management of CRPS was recommended as a strategy to prevent chronicity and possible central sensitization in order to improve pain,

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functional status, and outcome (9). A favorable outcome of CRPS is reported in some case studies where SCS was used in the first year of the syndrome (10,11). In a retrospective case series describing early SCS intervention in ten consecutive military personnel patients with CRPS of 5- to 12-month duration, significant reduction of pain and daily morphine requirements was reported. All patients became compliant with physical therapy and six returned to active duty. These initial findings suggested that early use of SCS, i.e., less than one year after the inciting event, improves functional outcome (12). We report on a prospective observational study where we investigated the feasibility of performing a randomized controlled clinical trial in which patients are treated with SCS within one year after the onset of CRPS and in which we studied the attributed beneficial effect of SCS on pain and functional outcome if applied early in the course of the disease, i.e., less than one year after the initiating event.

MATERIALS AND METHODS

Patients

In this prospective observational study, we screened all consecutive patients referred to our pain management center with a possible diagnosis of CRPS. Medical specialists and family physicians were informed by mail of the intention to start a study investigating the effect of SCS applied early in the course of CRPS-1 if patients did not obtain satisfactory pain reduction after standard therapy. They were asked to refer patients with severely painful CRPS-1 limited to one extremity, upper or lower, and in an early stage of the disease. Patients were eligible for the study if they had CRPS-1 according to the criteria established by the International Association for the Study of Pain (IASP) (1). Other inclusion criteria were the following: disease duration less than one year; signs/symptoms in one extremity only; no treatable underlying cause of the pain; age 18 years or older; able to follow written and verbal instructions; mean Numerical Pain Rating Score (NRS) according to Jensen and McFarland (13) of five or more on a scale from zero to ten (with zero meaning no pain at all and ten meaning the worst imaginable pain); and no pain reduction with persistent functional impairment after initial standard therapy. Exclusion criteria were the following: pregnancy, coagulation disorders, general infection, fever or local infection at the puncture site, drug or alcohol abuse, an implanted pacemaker, diabetic polyneuropathy, or any other disease that may account for signs and symptoms mimicking CRPS. Patients with an immune deficiency or patients using immunosuppressive drugs also were excluded. The study was approved by the Institutional Review Board of the Maastricht University Medical Centre, The Netherlands, and the St. Elisabeth Hospital in Tilburg, The Netherlands. All patients gave written informed consent.

Variables

Average week pain scores were derived from numerical pain ratings (NRS), assessed five days in a row, three times a day (13,14). We asked patients to fill in a pain assessment diary at home at baseline and for the SCS treated group at six weeks, three months, six months, and 12 months after the implantation.

Clinically important change was assessed using the Patient Global Impression of Change (PGIC), a seven-point ordinal scale used after treatment as an external criterion of clinical change (1 worst ever, 2 much worse, 3 worse, 4 no change, 5 improved, 6 much improved, and 7 best ever). The PGIC was translated into Dutch in accordance with international guidelines (15,16). PGIC measures

have been demonstrated to be valid indicators of clinically important change in CRPS patients (15,17).

Evoked pain was registered at baseline in three ways: the allodynia for touch by stroking the skin of the dorsal aspect of the affected foot or hand with a cotton wisp, the allodynia for pressure by gently squeezing the ankle fork or styloid processes of wrist, and the allodynia for movement by passive movement of the involved foot or hand. Tests were considered positive if they caused pain.

Quality of life (QoL) was assessed by means of the Dutch language version of the Short Form 36 (SF36) (18). Functional status was assessed with the Walking Questionnaire (WQ) and the Questionnaire Rising and Sitting Down (QRS) (19). The WQ consists of two scales, "walking inside the house" and "walking outside"; it measures the walking activity limitations in at home living patients with lower-extremity disorders (20).

Standard Therapy

According to CRPS treatment guidelines, all patients received early physical therapy aimed at active mobilization, according to a fixed protocol, which consisted of graded exercises aimed at restoring strength, mobility, and function of the affected extremity (21). Physical therapy was applied twice a week with a minimum duration of 30 min. Exercises were adjusted so that an increase of pain occurring during and after exercise returned to pre-session levels within 24 hours (22). Topical application of the free radical scavenger dimethyl sulfoxide (50%) three to five times daily was given as anti-inflammatory therapy. The physical therapy was supplemented with oral analgesic medication such as nonsteroidal anti-inflammatory drugs, acetaminophen, and tramadol. If no pain relief was obtained with at least three weeks of the analgesic medication, gabapentin was given in doses up to 1800 mg daily. No pain relief was defined as NRS unchanged or maximal one point improvement. If no pain relief was obtained after at least three weeks of gabapentin, transcutaneous electrical nerve stimulation (TENS) was applied during two weeks. If there was insufficient pain relief with these interventions, sympathetic blockade (SB), i.e., stellate ganglion block for the upper extremity and lumbar sympathetic block for the lower extremity, was applied (23,24). If patients had moderate to good pain relief after a test SB, the SB was repeated at least three times with one-week interval. SCS was offered if there still was considerable pain (NRS of five or more) with persistent functional impairment despite the standard therapy.

Test Stimulation and Implantation of the Spinal Cord Stimulator

All patients eligible for SCS received a test SCS according to our in hospital standard practice for a period of one-week home testing with a temporary percutaneous lead. This electrode (model 3861, Medtronic, Minneapolis, MN, USA) was placed epidurally under fluoroscopic guidance with the patient in the prone position. For lower-extremity CRPS-1 the tip of the electrode was placed at the Th10-11 level and for upper-extremity CRPS-1 the tip of the electrode was placed at the C3-4 level. After the testing period, the electrode was removed. A spinal cord stimulator was implanted within four weeks after the test stimulation period if patients responded to SCS therapy. Patients who did not respond to SCS therapy were treated with physical therapy alone. Standard implantation techniques as described earlier were used (25). Again in the prone position, a quadripolar electrode (model 3487A) was inserted in approximately the same location as the temporary lead but this time through a

5-cm vertical midline incision in the skin overlying the upper thoracic (for CRPS of the hand) or lumbar spine (for CRPS of the foot). After obtaining adequate stimulation patterns, the electrode was fixed to the lumbar fascia with an anchor after which the patient was placed in a left or right lateral decubitus position. General anesthesia was induced with propofol and sufentanil. A laryngeal mask was introduced subsequently. The electrode was connected by means of a tunneled extension lead (model 7495, 51/66) to an Itriel III pulse generator (model 7425) implanted in the right or left lower abdominal wall. The pulse generator was set at a frequency of 80 Hz and a pulse width of 210 μ sec. The patient could control the amplitude of the stimulator from 0 to 10 V with a patient programmer (model 7434). The patient was discharged the next day after adequate electrode positioning confirmation by x-ray and patient report of paresthesias covering the painful area of the involved limb.

Definition of a Responder to SCS Therapy

A responder is defined as a patient with a mean NRS pain score reduction of at least 50% during the last four home testing days of trial SCS and a PGIC score of six or seven (much improved or best ever) on a seven-point scale.

Data Collection and Follow-Up of the Spinal Cord Stimulated Group

Patient characteristics and variables were measured at baseline, six weeks, three months, six months, and 12 months after implantation. We asked the patients to fill in the diary and questionnaires at home and requested to bring the completed forms to the pain center.

Statistical Analysis

Mean weekly pain scores were calculated per patient. In the SCS treated group, mean total scores and change scores were calculated of the WQ and QRS. The data were processed and analyzed using the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Out of 147 patients with presumed CRPS, referred for this study between June 2005 and October 2008, 74 patients fulfilled the inclusion criteria. These 74 patients with CRPS-1 in one extremity and with a disease duration of less than 12 months (mean duration 17 weeks, range 2–50 weeks) received standard therapy with the possibility of early treatment with SCS in case of failure of this standard therapy. Fifty-five (74%) patients improved to a mean pain score of 2.1 (range zero to less than five) with standard therapy. Two patients with persistent severe pain scores of more than five after standard therapy were excluded because all other symptoms totally subsided and they did not meet the IASP CRPS-1 criteria anymore. One patient was excluded because, after standard therapy, symptoms existed for more than one year. Of the 12 patients eligible for early SCS, six patients (50%) refused the SCS treatment and withdrew from participation in the study. The remaining six patients underwent a test SCS (Fig. 1).

Spinal Cord Stimulated Group

All six patients in the SCS treated group were women with CRPS located in the lower extremities (Table 1). Mean age was 35 years

(standard deviation 17.5), and mean disease duration was 7.5 months with a range of five to ten months. The initiating event for CRPS was surgery, fracture, sprain, or the symptoms occurred spontaneously. Patients 1–3 did not meet the criteria for permanent SCS implantation (negative trial stimulation); patients 4–6 were implanted with a permanent device after a successful one-week trial. No complications requiring re-intervention occurred during the one-year follow-up period.

Pain

The evoked pain/allodynia at baseline was tested positive for pressure and movement in all six patients and for touch in three of the six patients.

After the SCS trial period of one week, four out of the six patients had an improvement in mean pain score (Fig. 2). Three patients met more than 50% pain reduction inclusion criteria for permanent implantation. There was an overall mean pain relief of 35% after one year. Four patients had a mean pain reduction of at least two points, in one patient pain decreased with one point, and one patient had an increase in mean pain (+2.1). The initially observed greater pain reduction in the patients with a permanent SCS, compared with the patients not permanently treated with SCS, evened out after one year.

PGIC

PGIC was assessed by patients at six weeks, three months, six months, and 12 months after trial SCS. After one year, two patients scored much improved and one patient scored unchanged in the implanted group. In the not implanted group, two patients scored much improved and one patient scored worse.

QoL

In patients treated with SCS in the early phase of the disease, there was improvement in mental well-being as measured by the SF36 Mental Component Summary. There was no clear effect on physical functioning (SF36 Physical Component Score) (Table 2).

Functional Status

Functional status was assessed with the WQ and QRS (Table 3). One (not implanted) patient showed an improvement in walking function outside the house but not in walking in the house. All others showed no improvement in walking function either in the house or outside. It is noticeable that all patients show worsening of function in rising and sitting down (QRS) after one year of treatment.

DISCUSSION

Of the 74 patients with early CRPS-1, 55 (74%) patients improved to a mean pain score of 2.1 (range zero to less than five) after the initial standard treatment, thus no longer qualifying for early intervention with SCS therapy. Only six patients during a three-year period could eventually be included for early SCS, making the study underpowered and making it impossible to draw firm conclusions as to the effectiveness of SCS in the early stage of CRPS-1. The standard therapy as described in the methods section could take up to nine weeks before patients were offered SCS treatment. The positive

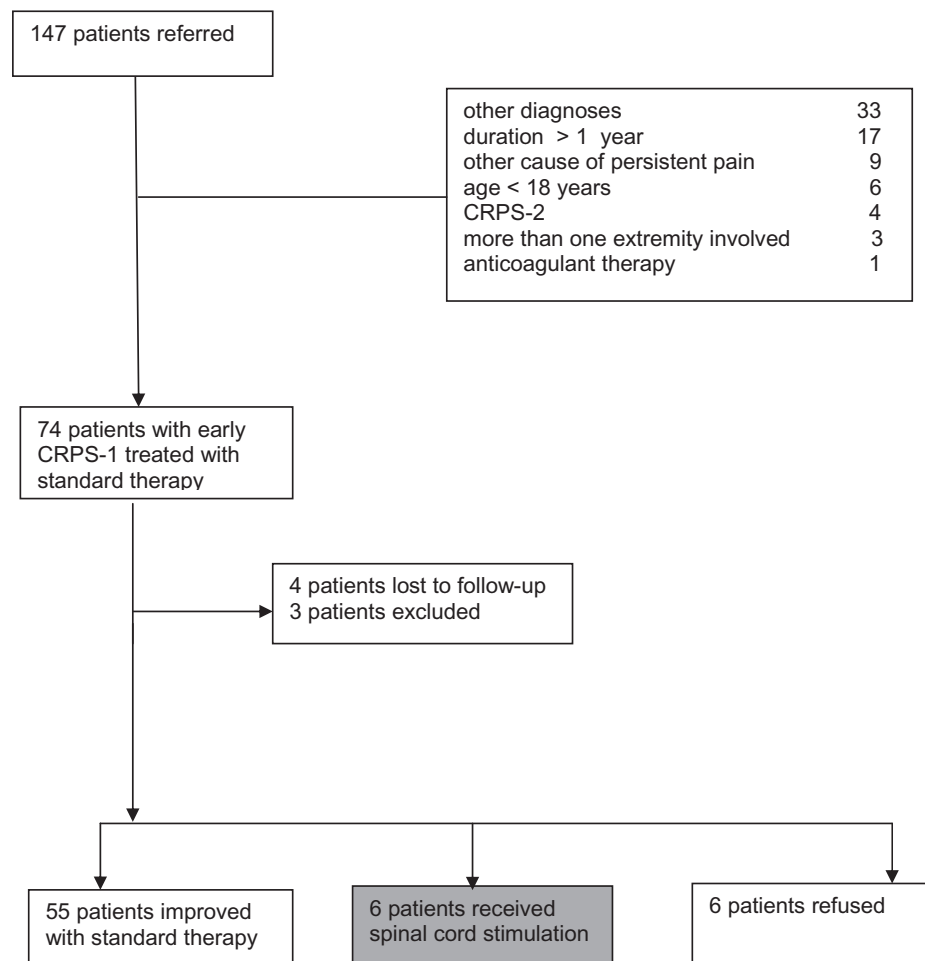


Figure 1. Flow chart of referred patients. CRPS, complex regional pain syndrome.

Table 1. Patient Characteristics.

Patient	Gender	Age (years)	CRPS location	Duration CRPS (months)	Initial trauma	Trial pain relief (%)	Endpoint pain relief (one year) (%)
1	Woman	55	Right leg	5	Surgery	13.3	20.7
2	Woman	60	Right leg	7	Fracture	45.1	30.7
3	Woman	21	Left leg	10	Sprain	10.1	37.4
4 SCS	Woman	27	Left leg	5	Surgery	60.1	47.0
5 SCS	Woman	23	Left leg	9	Spontaneously	52.4	36.6
6 SCS	Woman	25	Left leg	9	Sprain	50.6	38.7

CRPS, complex regional pain syndrome; SCS, spinal cord stimulator, permanently implanted.

outcome of so many early CRPS-1 patients after standard therapy, i.e., 74%, was unanticipated at the start of the study. The power analysis for a randomized controlled trial (RCT) comparing early SCS treatment with a control group estimated a sample size of 64 patients. To include 64 patients without improvement after standard treatment, about 800 patients with early CRPS-1 should be screened. Given the incidence rate of approximately 16 (5–26) per 100,000 person years and the catchment area of our institutions for early CRPS-1 patients of 500,000, ten years of inclusion would be needed (2,3). We therefore conclude that the feasibility of performing a proper RCT that questions the efficacy of early SCS is low.

In the patients treated with early SCS, a mean of 35% pain reduction was obtained, and an improvement in mental but not in functional outcome was seen. These observations are comparable with earlier observations in a chronic CRPS-1 population (8). Moreover, we found no indication that the percentage of responders (three out of six) to SCS therapy in the early phase of CRPS-1 (mean duration of CRPS-1 of 7.5 months, range five to ten months) is any different than in the chronic CRPS-1 population (mean duration of CRPS-1 of 40 months, range 12–68 months) where two out of three patients were responders to SCS therapy (8). It should be noted that all our patients had no pain relief after sympathetic block and thus

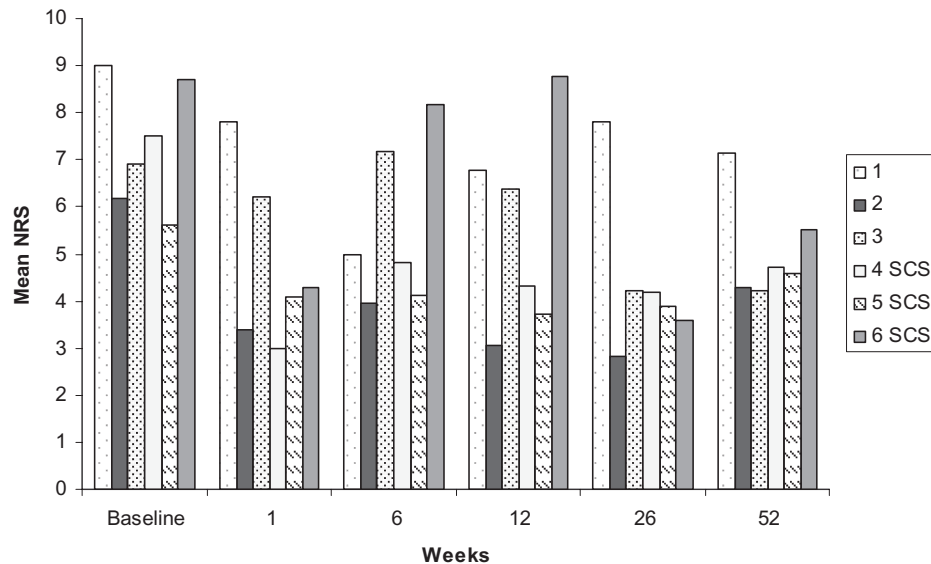


Figure 2. Mean pain scores (NRS) assessed at baseline and 1, 6, 12, 26, and 52 weeks after trial SCS. NRS, Numerical Pain Rating Score; SCS, spinal cord stimulation.

Table 2. SF36 Quality of Life.

	MHS baseline		MHS one year		PHS baseline		PHS one year	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SCS	50.7	13.1	64.0	8.7	23.7	12.7	23.7	2.5
NI	56.5	14.8	46.7	11.7	35.5	12.7	35.3	2.1

SCS, spinal cord stimulation; NI, not implanted; MHS, Mental Component Summary; PHS, Physical Component Summary; SD, standard deviation; SF36, Short Form 36.

could be qualified as having sympathetically independent pain. In a study of 29 chronic CRPS-1 patients of more than one-year duration with sympathetically maintained pain (SMP), demonstrated by a positive short lasting pain relieving response to sympathetic block, patients showed not only pain relief but also improvement in functional status after treatment with SCS (26). The positive effect of SCS in SMP was demonstrated by the reversal of the vasoconstriction and reduced blood flow with activation of the SCS (26). This effect on the microcirculation could not be demonstrated in patients with CRPS-1 associated sympathetically independent pain (27). In our study, we used the older quadripolar electrodes because the newer octapolar electrodes were not yet routinely available at the time of inclusion. We doubt, however, that results would be any different if the newer octapolar electrodes had been used because the area of pain was adequately covered by paresthesia in all SCS treated patients.

The large number of drop outs in our patient group (six out of 12 or 50%) may be due to the relatively brief duration of CRPS-1 at the time when patients are offered to be treated with SCS. There seems to be considerable hesitation to undergo such a kind of invasive treatment early in the course of the disease. Our findings raise questions about the better outcome of CRPS-1 patients with associated sympathetically independent pain when intervention with SCS is applied early in the course of the disease. Others found SCS to be extremely successful in the treatment of early CRPS (12). The degree of pain reduction obtained with SCS in a group of ten consecutive CRPS patients was considerably higher with a mean of 79% pain reduction (pain score 7.8 ± 1.3 to pain score 1.6 ± 1.5) vs. only 35%

pain reduction in our implanted group. The higher pain reduction indeed would allow for a better compliance with physical therapy and a better functional outcome (12). The lesser pain reduction in our early stimulated patients also could be related to central sensitization. All six patients indeed had allodynia at the baseline assessment. From surgical postoperative pain research, we know that nociception-induced central sensitization mediated through the involvement of excitatory amino acids via the N-methyl-D-aspartate receptor may start during and in the first hours after surgery. This process moves from activation and modulation of the central nervous system (CNS) to modification of the CNS and chronic pain (28). Experimental work has shown that central sensitization is a key event during the development of neuropathic pain. Central sensitization of somatosensory neurons in the dorsal horn of the spinal cord refers to an increased synaptic activity established in these neurons (29). This activity dependent central sensitization, which often is initiated by an increased glutamate release in the dorsal horn, can develop within hours-days (30). The modulatory effect of SCS on neuropathic pain is suggested to act via a temporal decrease in glutamate concentrations in the dorsal horn, as was found in neuropathic rats (31). Early SCS treatment within the first days, when central sensitization is characterized by only short-term reversible changes, may result in a better outcome. Results from the laboratory indicate that SCS in Seltzer injured rats 24 hours after injury and development of neuropathic pain result in a better outcome as compared with the treatment after 16 days (32). Long-term more permanent changes, related to central sensitization, also may underlie the fact that SCS is less effective when brush evoked

Table 3. Total Scores and Difference Scores of Baseline and Endpoint Measurement for Changes in Functional Impairment.

Patient	WQ/QRS	WQ/QRS		Endpoint comparison Difference*
		Baseline	Endpoint (one year)	
1	WH	5.2	5.9	-0.7
	WO	8.9	6.5	2.4
	RS	1.8	8.4	-6.6
2	WH	6.5	5.9	0.6
	WO	8.7	8.7	0.0
	RS	8.4	10.0	-1.6
3	WH	7.6	7.6	0.0
	WO	10.0	10.0	0.0
	RS	6.3	6.8	-0.5
4 SCS	WH	10.0	10.0	0.0
	WO	10.0	10.0	0.0
	RS	10.0	10.0	0.0
5 SCS	WH	4.7	7.1	-2.4
	WO	6.1	7.0	-0.9
	RS	3.2	9.5	-6.3
6 SCS	WH	5.3	5.9	-0.6
	WO	6.1	7.0	-0.9
	RS	3.2	7.9	-4.7

*Values reflect worsening of functional impairment.
WH, walking in the house; WO, walking outside; RS, rising and sitting down; SCS, spinal cord stimulation; QRS, Questionnaire Rising and Sitting Down; WQ, Walking Questionnaire.

allodynia is present (25). In clinical practice, however, it is impossible to treat CRPS-1 patients with SCS within days after development of the syndrome because it usually takes weeks or months before a diagnosis is made.

Another issue is the good clinical improvement with standard care. In our group, 74% of patients improved with standard therapy. In another study of 168 patients diagnosed with CRPS according to the modified IASP criteria, 121 (72%) had a successful outcome with physical therapy, medical therapy, and SB (33). Whether this improvement reflects the effects of therapy or the natural course of the disease is hard to tell because there are no controlled prospective studies on the outcome of early CRPS-1. The excellent improvement within one year after onset of CRPS using standard therapy, i.e., physical and analgesic therapy, TENS, and SB, together with the possible lack of additional benefit from the SCS argues against any early intervention with SCS therapy in CRPS-1. If the pain and disability persist at one year after onset of the syndrome, the chance of successful recovery is significantly reduced, and SCS may be considered. In a group of 656 patients with CRPS of at least one-year duration, none showed spontaneous remission with high average pain intensity scores of 6.91 ± 0.5 , which increased significantly with disease duration to 7.92 ± 0.6 (4).

We conclude that the feasibility of doing a study on SCS therapy in early CRPS-1 is low because of the good improvement of the disease with standard therapy. This study raises questions about the need to use SCS early in the course of CRPS-1 because of the possible lack of additional benefit compared with SCS in chronic CRPS-1.

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Authorship statements

All authors designed and conducted the study, including patient recruitment, data collection, and data analysis. Dr. van Eijs and Dr. J. Geurts prepared the manuscript draft with important intellectual input from Dr. C. Faber, Dr. A. Kessels, Dr. E. Joosten, Dr. van Zundert, and Prof Dr. M. van Kleef. All authors approved the final manuscript. TREND and Maastricht University Medical Center department of anesthesiology provided funding for the study, statistical support in analyzing the data with input from Dr. J. Geurts and Dr. A. Kessels, and also provided funding for editorial support. Dr. F. van Eijs, Dr. J. Geurts, and Dr. A. Kessels had complete access to the study data. We would like to thank Dr. R. Perez for his intellectual input and Mrs. N. van den Hecke for her editorial support during preparation of this manuscript.

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REFERENCES

- Merksey BN, Bogduk N. *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms*, 2nd ed. Seattle, WA: IASP Press, 1994.
- de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: a population-based study. *Pain* 2007;129:12–20.
- Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *Pain* 2003;103:199–207.
- Schwartzman RJ, Erwin KL, Alexander GM. The natural history of complex regional pain syndrome. *Clin J Pain* 2009;25:273–280.
- de Mos M, Huygen FJ, van der Hoeven-Borgman M, Dieleman JP, Ch Stricker BH, Sturkenboom MC. Outcome of the complex regional pain syndrome. *Clin J Pain* 2009;25:590–597.
- Stanton-Hicks MD, Burton AW, Bruehl SP et al. An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. *Pain Pract* 2002;2:1–16.
- Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. *Eur J Pain* 2006;10:91–101.
- Kemler MA, Barendse GA, van Kleef M et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med* 2000;343:618–624.
- Stanton-Hicks M. Complex regional pain syndrome: manifestations and the role of neurostimulation in its management. *J Pain Symptom Manage* 2006;31:S20–S24.
- Harney D, Magner JJ, O'Keefe D. Early intervention with spinal cord stimulation in the management of a chronic regional pain syndrome. *Ir Med J* 2005;98:89–90.
- Saranita J, Childs D, Saranita AD. Spinal cord stimulation in the treatment of complex regional pain syndrome (CRPS) of the lower extremity: a case report. *J Foot Ankle Surg* 2009;48:52–55.
- Verdolin MH, Stedje-Larsen ET, Hickey AH. Ten consecutive cases of complex regional pain syndrome of less than 12 months duration in active duty United States military personnel treated with spinal cord stimulation. *Anesth Analg* 2007;104:1557–1560.
- Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. *Pain* 1993;55:195–203.
- Jensen MP, Turner JA, Romano JM. What is the maximum number of levels needed in pain intensity measurement? *Pain* 1994;58:387–392.

15. Forouzanfar T, Weber WE, Kemler M, van Kleef M. What is a meaningful pain reduction in patients with complex regional pain syndrome type 1? *Clin J Pain* 2003;19:281–285.
16. Streiner D, Norman G. *Health measurement scales. A practical guide to their development and use*, 2nd ed. New York: Oxford University Press, 1998.
17. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical scale. *Pain* 2001;94:149–158.
18. Aaronson NK, Muller M, Cohen PD et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055–1068.
19. Perez RS, Roorda LD, Zuurmond WW, Bannink II, Vranken JH, de Lange JJ. Measuring perceived activity limitations in lower extremity complex regional pain syndrome type 1 (CRPS I): test-retest reliability of two questionnaires. *Clin Rehabil* 2002;16:454–460.
20. Roorda LD, Roebroeck ME, van Tilburg T et al. Measuring activity limitations in walking: development of a hierarchical scale for patients with lower-extremity disorders who live at home. *Arch Phys Med Rehabil* 2005;86:2277–2283.
21. Stanton-Hicks M, Baron R, Boas R et al. Complex regional pain syndromes: guidelines for therapy. *Clin J Pain* 1998;14:155–166.
22. Oerlemans HM, Oostendorp RA, de Boo T, Goris RJ. Pain and reduced mobility in complex regional pain syndrome I: outcome of a prospective randomised controlled clinical trial of adjuvant physical therapy versus occupational therapy. *Pain Pract* 2011;11(1):70–87.
23. Albazaz R, Wong YT, Homer-Vanniasinkam S. Complex regional pain syndrome: a review. *Ann Vasc Surg* 2008;22:297–306.
24. van Eijs F, Stanton-Hicks M, Van Zundert J et al. Complex regional pain syndrome. *Pain Pract* 2011;11(1):70–87.
25. van Eijs F, Smits H, Geurts JW et al. Brush-evoked allodynia predicts outcome of spinal cord stimulation in complex regional pain syndrome type 1. *Eur J Pain* 2010;14:164–169.
26. Harke H, Gretenkort P, Ladleif HU, Rahman S. Spinal cord stimulation in sympathetically maintained complex regional pain syndrome type I with severe disability. A prospective clinical study. *Eur J Pain* 2005;9:363–373.
27. Kemler MA, Barendse GA, van Kleef M, Egbrink MG. Pain relief in complex regional pain syndrome due to spinal cord stimulation does not depend on vasodilation. *Anesthesiology* 2000;92:1653–1660.
28. Wilder-Smith OH, Arendt-Nielsen L. Postoperative hyperalgesia: its clinical importance and relevance. *Anesthesiology* 2006;104:601–607.
29. Cook AJ, Woolf CJ, Wall PD, McMahon SB. Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent input. *Nature* 1987;325:151–153.
30. Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends Neurosci* 2003;26:696–705.
31. Cui JG, O'Connor WT, Ungerstedt U, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates augmented dorsal horn release of excitatory amino acids in mononeuropathy via a GABAergic mechanism. *Pain* 1997;73:87–95.
32. Truin M, van Kleef M, Linderoth B, Smits H, Janssen S, Joosten E. Increased efficacy of early spinal cord stimulation compared to late spinal cord stimulation in an animal model of neuropathic pain. *Eur J Pain* 2011;15(2):111–117.
33. Duman I, Dincer U, Taskaynatan MA, Cakar E, Tugcu I, Dincer K. Reflex sympathetic dystrophy: a retrospective epidemiological study of 168 patients. *Clin Rheumatol* 2007;26:1433–1437.

COMMENTS

Early treatment of ongoing pain is probably the key. All studies focusing on this period will be difficult to organize as it requires a longitudinal network of specialists. The result of this study is relevant also in this regard.

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The authors of this study bring us a few small steps further in our understanding of the many factors that determine how successful a therapeutic response to SCS will be. Their results confirm anecdotal and scientific wisdom that SMP is advantageous and that central sensitization may impair the therapeutic response of SCS. Mechanical allodynia as already published by the same group is another confounding factor in the outcome response (1). Perhaps contemporary equipment might have improved their end-points, but again we have no side-by-side comparisons of equipment and the rest is up to conjecture. We need many more studies of this caliber.

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REFERENCE

1. Van Eijs F et al. Brush-evoked allodynia predicts outcome of spinal cord stimulation in complex regional pain syndrome type I. *Eur J Pain* 2010;14:164–169.

Comments not included in the Early View version of this paper.