

Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial

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Object. Chronic complex regional pain syndrome–Type I (CRPS-I) is a painful, disabling disorder for which no treatment with proven effect is available. In the present randomized controlled trial, the authors assessed the effectiveness of spinal cord stimulation (SCS) in reducing pain due to CRPS-I at the 5-year follow-up.

Methods. The authors performed a randomized trial in a 2:1 ratio in which 36 patients with CRPS-I were allocated to receive SCS and physical therapy (PT) and 18 patients to receive PT alone. Twenty-four patients who received SCS+PT also underwent placement of a permanent spinal cord stimulator after successful test stimulation; the remaining 12 patients did not receive a permanent stimulator. The authors assessed pain intensity, global perceived effect, treatment satisfaction, and health-related quality of life. Patients were examined before randomization, before implantation, and every year until 5 years thereafter. Ten patients were excluded from the final analysis.

Results. At 5 years posttreatment, SCS+PT produced results similar to those following PT for pain relief and all other measured variables. In a subgroup analysis, the results with regard to global perceived effect ($p = 0.02$) and pain relief ($p = 0.06$) in 20 patients with an implant exceeded those in 13 patients who received PT.

Conclusions. Despite the diminishing effectiveness of SCS over time, 95% of patients with an implant would repeat the treatment for the same result. (DOI: 10.3171/JNS.2008.108.2.0292)

KEY WORDS • electric stimulation therapy • randomized trial • reflex sympathetic dystrophy • spinal cord

TREATMENT of CRPS-I is mostly very disappointing.^{13,31} This syndrome of unknown pathophysiology, which usually commences after trauma or operation on a limb, results in pain, functional impairment, and trophic changes. Its incidence has been reported as 5.46 cases per 100,000 person-years at risk, and the period prevalence as 20.57 cases per 100,000 person-years at risk.³² In chronic cases, reflex sympathetic dystrophy leads to extreme pain, disability, and inability to work, thus dramatically changing the lives of patients as well as their families.^{21,25}

We performed a prospective randomized controlled trial to determine whether the treatment of chronic CRPS-I with SCS and PT is more effective than PT alone. In SCS, an electrode is positioned in the epidural space on the dorsal aspect of the spinal cord at the level of the nerve roots innervating the painful area.

Electrical current from the electrode brings about paresthesia, a sensation that suppresses the pain. At both the 6-month and 2-year follow-ups, data have demonstrated that SCS reduces severe burning pain, which is characteristic of the syndrome, by more than 50%;^{19,22} however, it does not influence allodynia, hypesthesia, or function.^{19,22,26}

Although implanting a SCS system is an expensive and invasive treatment accompanied by a high percentage of complications, it has been shown to be less costly than the standard treatment protocol after 3 years of successful therapy.²⁴ Note, however, that the only results presented to date have been from a maximum of 2 years of follow-up.

In a brief letter, we reported that a 5-year follow-up analysis revealed that the pain-alleviating effect of SCS in chronic CRPS-I diminishes over time and that compared with results in a control group, this effect is no longer significant after 3 years of follow-up.²³ In the current paper, we present explanations for this decrease in pain relief and the effects on other outcome measures, such as global perceived effect, patient satisfaction, and health-related QOL. A randomized controlled trial with 5 years of follow-up is

Abbreviations used in this paper: CRPS-I = complex regional pain syndrome–Type I; EQ-5D = EuroQol-5D; PT = physical therapy; QOL = quality of life; SCS = spinal cord stimulation; SD = standard deviation; VAS = visual analog scale.

Spinal cord stimulation in CRPS-I

especially interesting because it concerns an invasive intervention for a chronic syndrome. Moreover, such a long follow-up is quite unique, for both CRPS-I and SCS.

Clinical Material and Methods

Selection of Patients

Inclusion in the study was considered in patients meeting the International Association for the Study of Pain criteria for CRPS-I, including 1) the presence of an initiating noxious event or cause of immobilization; 2) continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to the inciting event; 3) evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain; and 4) the absence of conditions that would otherwise account for the degree of pain and dysfunction.³⁰ Additional inclusion criteria were as follows: an age of 18–65 years; disease clinically restricted to one extremity but affecting the whole hand or foot; disease duration of at least 6 months; no lasting success with standard therapy, including 6 months of PT, sympathetic blocks, transcutaneous electrical nerve stimulation, and medication; and a mean pain intensity of at least 5 cm, as measured on a VAS from 0 (no pain) to 10 cm (very severe pain), as described by Jensen and McFarland.¹⁶ Exclusion criteria consisted of the presence of Raynaud disease; the presence, or a history, of neurological abnormalities unrelated to CRPS-I; conditions other than CRPS-I affecting the function of diseased or contralateral extremities; blood clotting disturbances or anticoagulation drug therapy; cardiac pacemaker use; and a score of 200 or more on the Symptom Check List-90,¹ a standardized psychological test. The study protocol complied with the Declaration of Helsinki regarding investigations in humans and was approved by the medical ethics committee of Maastricht University Hospital. All patients gave written informed consent.

Randomization and Power Calculation

Through randomization patients were assigned to a treatment group: either SCS plus a standardized PT program (SCS+PT group) or a standardized PT program alone (PT group). At the end of the baseline assessment, a concealed randomization procedure was applied, with prestratification for the location of the syndrome (upper or lower extremity). The patient was assigned to the SCS+PT or PT group by an uninvolved person who contacted the patient via telephone and who made use of a computer-generated table of random numbers. The randomization involved a 2:1 ratio in favor of the SCS+PT group. All patients assigned to SCS+PT underwent test stimulation; those who did not respond positively to this treatment did not subsequently undergo implantation of the SCS system.

To estimate the required sample size, pilot study data were used.²⁰ The prespecified study aim was to detect significant pain relief of 3.5 cm at 6 months in patients with an implanted spinal cord stimulator. Given that 33% of patients allocated to the SCS+PT group were expected to have no reaction to test stimulation (improvement 0), pain reduction in the SCS+PT group, which we aimed to detect in this study, was 2.3 cm ($0.66 \times 3.5 + 0.33 \times 0$). Using the SD (± 2.34) from the pilot study, 51 (34 + 17) patients

are needed in a 2:1 randomization scheme to detect a 2.3 cm difference between the treatment groups at a two-tailed significance (α) level of 0.05 and a power of 0.90.

Test Stimulation and Implantation Criteria

There was a home-testing period of at least 7 days to determine whether patients responded positively to SCS. The operative procedures related to implanting for the test and permanent stimulation systems have been described previously.¹⁹ The decision to implant the permanent SCS system was made when pain intensity measured during the last 4 days of the testing period was at least 50% lower as compared with the baseline VAS score, or if “much improvement” (6 points) was reported on a 7-point global perceived effect scale. Patients not meeting these criteria continued the study with PT alone.

Physical Therapy Program

The PT program was offered to all patients and consisted of exercises involving a graded activity approach aimed to improve endurance, mobility, and function of the affected extremity. The program lasted 6 months, although continuation thereafter was optional. Details of the program have been described previously.²⁷

Data Collection and Follow-Up

Patients were assessed before randomization (baseline) and on the day prior to implantation (start of treatment). Assessments at the start of treatment in patients not receiving an implant were planned to occur close to the start of treatment in those who did. Further assessments were made at 1 (T1), 3 (T3), 6 (T6), 12 (T12), 24 (T24), 36 (T36), 48 (T48), and 60 months (T60) after the start of treatment. Outcome measures were grouped into four categories. First, pain was assessed using a VAS developed by Jensen and McFarland¹⁶ (primary outcome measure) and the McGill Pain Questionnaire, expressed as the number of words chosen and the pain rating index.²⁹ Second, patients rated global perceived effect on a 7-point scale: worst ever (1 point), much worse (2 points), worse (3 points), not improved/not worse (4 points), improved (5 points), much improved (6 points), and best ever (7 points).¹² At the final follow-up, the patients who had received an implant were asked whether the treatment had a positive effect and whether they would repeat the treatment for the same result. Third, we measured health-related QOL using the Nottingham Health Profile,¹⁵ the Sickness Impact Profile-68,⁷ the EQ-5D,³⁴ and the Self-Rating Depression Scale.³⁹ These questionnaires had previously been validated and translated into Dutch.^{6,8,38} Each patient's EQ-5D ratings were transformed into a utility (that is, a preference score that the general public would give for the health state as indicated by the patient). The relative valuations of members of the general public in different states of health (that is, the EQ-5D ratings) were derived from Dolan⁹ and have been elicited using the time trade-off.¹⁰ Fourth, we listed technical and surgical complications.

Statistical Analysis

For all outcome measures, differences between the start of treatment and T60 values for each individual were cal-

culated and compared between treatment groups by using independent sample t-tests or, if the results were not normally distributed, nonparametric tests. Fisher exact tests were used to compare proportions. For the global perceived effect (dichotomized as \geq much improved and \leq improved), no baseline information exists; consequently, only differences between the two groups at T60 were calculated. Multivariate regression analysis was performed to assess the potential influences of baseline differences in prognostic factors and outcome variables on the magnitude of the effect. Two-tailed probability values < 0.05 were considered to indicate statistical significance.

Previous statistical analyses of short-term results were performed according to the intention-to-treat principle. Here, in our main analysis, patients in the control group who had received an SCS implant or those who were lost to follow-up were excluded. In two additional analyses, we determined the influence of excluding certain patients: in one, we evaluated the last relevant data in the original 54 patients; and in another, we examined the last available data before implantation in patients who received an implant at a later stage after PT. Furthermore, a subgroup analysis was performed to compare patients who had received an implanted stimulator with those who had undergone PT alone.

Results

Between March 1997 and July 1998, 110 potential candidates were referred to our department. We included 54 patients, whereas 56 patients were excluded: 40 were not eligible, and 16 refused to participate. Randomization was successful, and the two groups were comparable at baseline with regard to all prognostic variables and outcome measures (data presented previously).^{19,26} The flowchart illustrating the study protocol is featured in Fig. 1. Ten patients were excluded from the 5-year analysis. Among patients assigned to the PT group, 4 were excluded after receiving a spinal cord stimulator, and 1 was lost to follow-up. Among patients assigned to the SCS+PT group, 4 were lost to follow-up, and 1 in whom it had been impossible to place a lead in the epidural space was excluded after receiving a special lead after 6 months. Thus, in the main 5-year follow-up analysis, we compared 31 patients in the SCS+PT group with 13 patients in the PT group.

Test Stimulation

Test stimulation was successful in 24 (67%) of 36 patients; all reported much improvement on the global perceived effect scale. In 19 patients, we measured a 50% decrease in the original VAS score.

Main Analysis

The 5-year (T60) results are reported in Table 1. After 5 years (results at T60 minus results at the start of treatment), the mean pain intensity following SCS+PT was reduced by 1.7 cm, compared with a reduction of 1.0 cm following PT ($p = 0.25$; Fig. 2). At 3 (−1.6 cm compared with −0.7 cm; $p = 0.29$) and 4 years (−1.7 cm compared with −1.0 cm; $p = 0.42$) of follow-up, similar results were obtained. At 5 years, among 31 patients in the SCS+PT group, 7 (23%) reported much improvement, compared with 2 (15%) of 13 patients in the PT group ($p = 0.24$; Fig. 3). At 5 years, SCS

was successful in 11 (35%) of 31 patients: 7 reported much improvement on the global perceived effect scale, 3 reported improvement, and 1 was not improved/not worse; and 7 showed a 50% decrease in the VAS score at the start of treatment, 1 a 6% increase, 1 no change, 1 a 35% decrease, and 1 a 48% decrease. Observed changes in other pain measures or health-related QOL tests were not statistically significant between the treatment groups. Multivariate regression analysis demonstrated that no baseline factor, except for treatment group, influenced the magnitude of the effect.

To demonstrate the influence of excluded patients, 2 alternative analyses were performed (Table 2): 1 involving the last available outcomes in all 54 patients and another involving the last available outcomes in 31 patients in the SCS+PT group compared with 17 patients in the PT group (before implantation of a stimulator in 4 patients from the PT group). These analyses did not reveal significant differences between the SCS+PT and PT groups.

Results in Patients With a Permanent SCS System

Two patients with an implanted spinal cord stimulator were lost to the 5-year follow-up. Two other patients underwent permanent removal of the stimulator on the grounds of recurrent rejection or relapsing ulcerative colitis ascribed to the system.^{17,18} The mean pain relief (VAS) score in the remaining 20 patients with a permanent implant was 2.5 cm, as compared with a 1.0-cm change among the 13 patients receiving PT ($p = 0.06$; Table 1). Much improvement was reported by 7 (35%) of 20 patients with an implant, compared with 2 (15%) of 13 patients receiving PT ($p = 0.02$). Spinal cord stimulation did not influence any of the health-related QOL scores. Nevertheless, 18 (90%) of 20 patients with an implant indicated that they had positively responded to the treatment, and 19 patients (95%) reported that they would undergo the treatment again for the same result.

After 2 years of follow-up, we reported a complication rate of 38%; 9 of 24 patients underwent reoperation for 21 complications.²² During treatment Years 3, 4, and 5, 8 complications requiring reintervention occurred in 4 of 20 patients (Table 3). Overall, during 5 years of treatment, 10 (42%) of 24 patients underwent reoperation as a result of 29 complications.

Pulse generators were replaced 4 times in 1 patient, 2 times in another, and once in 11 patients. Two patients underwent permanent explantation, 2 patients were lost to follow-up, and 7 patients still had their first pulse generator at the final follow-up. Taken together, the 36 patients in the SCS+PT group needed 42 pulse generators (24 first implants + 17 replacements + 1 reimplantation after an explantation due to infection) during 5 years of treatment, which indicates a mean battery life of approximately 4 years per patient. This battery life is in line with the estimated battery life that was used in an economic analysis. The longevity of pulse generators in patients with a cervical electrode (affected hand) was comparable to that in patients with a lumbar device (affected foot).

Discussion

This long-term follow-up analysis demonstrates that the

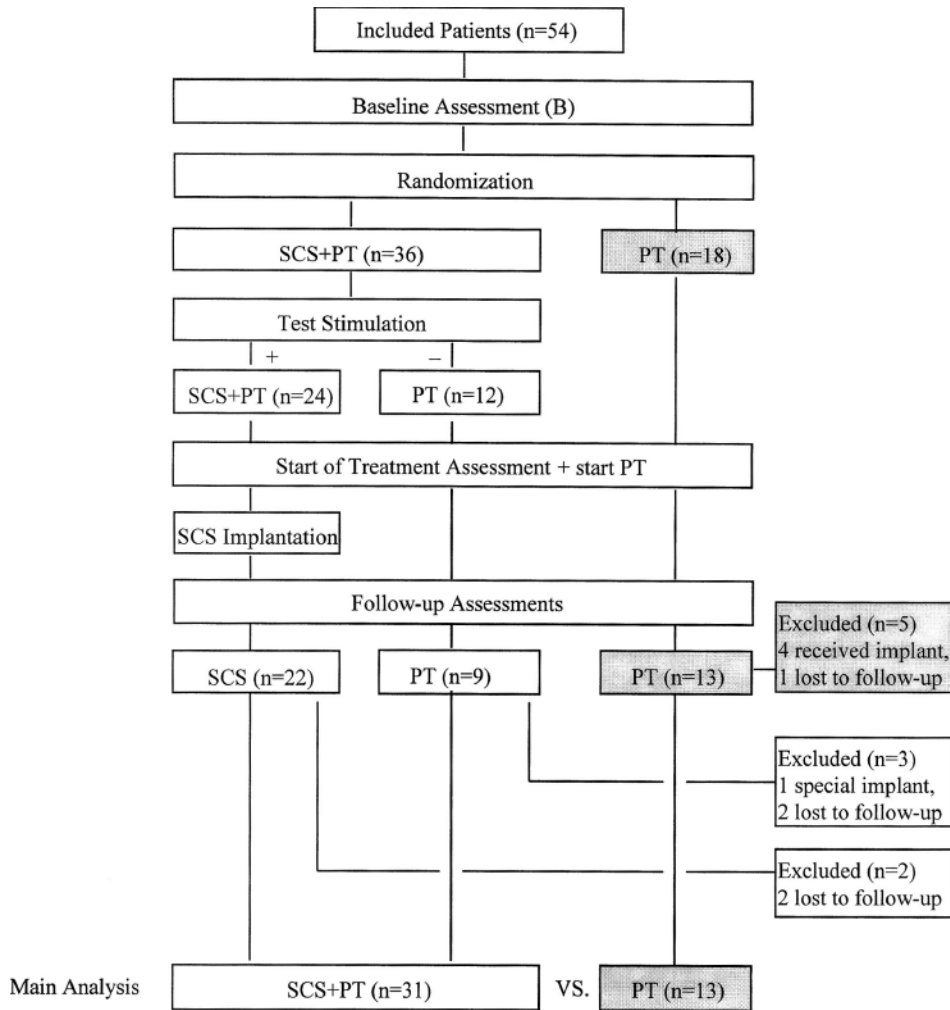


FIG. 1. Flowchart illustrating the study protocol and indicating the groups compared in the main and subgroup analysis. n = number of patients; - = negative response; + = positive response.

TABLE 1
Change in outcomes between the start of treatment and the 5-year follow-up*

Characteristic	Main Analysis			Subgroup Analysis	
	SCS+PT	PT	p Value†	Permanent Implant	p Value‡
no. of patients	31	13		20	
mean VAS score (cm)	-1.7 ± 2.3	-1.0 ± 2.9	0.25	-2.5 ± 2.2	0.06
no. of patients w/ ≥ much improved GPE (%)	7 (23)	2 (15)	0.24	7 (35)	0.02
health-related QOL measures (%)					
Nottingham Health Profile					
mobility	7 ± 15	5 ± 28	0.81	6 ± 15	0.93
pain	-7 ± 27	-5 ± 27	0.82	-15 ± 25	0.31
sleep	-15 ± 30	-12 ± 34	0.74	-22 ± 35	0.40
energy	5 ± 43	2 ± 55	0.88	12 ± 35	0.57
social isolation	4 ± 18	1 ± 20	0.66	5 ± 18	0.49
emotional reaction	-2 ± 27	-5 ± 26	0.74	-6 ± 26	0.88
EQ-5D	16 ± 25	19 ± 46	0.80	24 ± 26	0.73
Self-Rating Depression Scale	0 ± 9	-3 ± 11	0.47	-1 ± 8	0.66

* Values represent the means ± SD. Abbreviation: GPE = global perceived effect.

† The SCS+PT group compared with the PT group.

‡ The permanent implant group compared with the PT group.

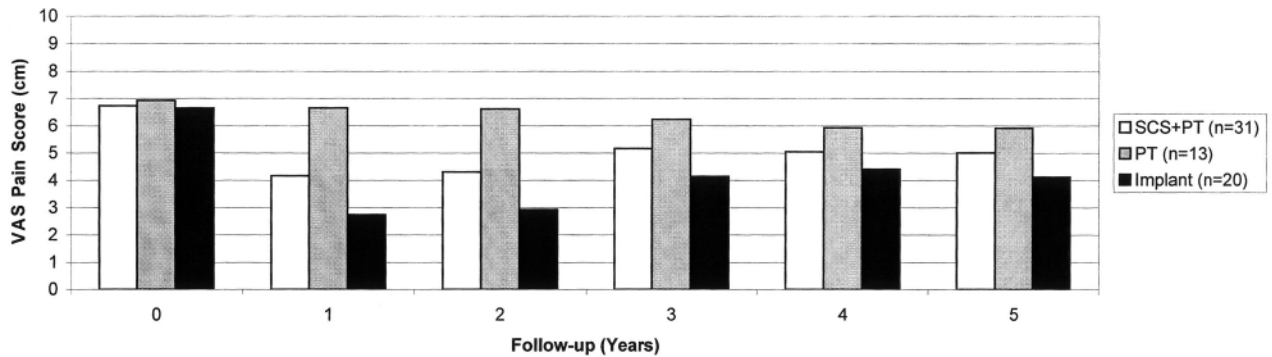


FIG. 2. Bar graph demonstrating the mean (\pm SD) VAS pain scores in patients with complex CRPS-I. The groups in the main analysis are represented by *white* and *gray bars*, whereas the subgroup of patients with an implant at the final follow-up is represented by *black bars*.

pain-alleviating effect of SCS in patients with chronic CRPS-I diminishes over time, compared with results in a control group, and is no longer significant at 3 years of follow-up. Among patients with an implanted system after 5 years of follow-up, however, 95% reported that they would be willing to go through the treatment again for the same result.

The reducing effectiveness of SCS can be explained by several factors. First, over time there is a true pain increase in the group treated with SCS. The unknown working mechanisms of the treatment³⁻⁵ apparently do not function indefinitely. Second, knowing that the actual implantation of a system fully depends on their response during trial stimulation, some patients might have exaggerated the effect in the first phase of treatment. Third, the unusual duration of the follow-up in our study made it possible to demonstrate that even patients in the control group have the potential for spontaneous improvement. Two such patients even reported at the final follow-up that their pain had disappeared completely. Although this is positive news for patients with chronic CRPS-I, in an intention-to-treat analysis, an improved condition in the control group of course affects the interpretation of the effect of SCS. The fact that only 4 of 18 control volunteers had switched to SCS at the

final follow-up further supports the notion that patients with chronic CRPS-I can experience improvement spontaneously. The effect of excluding these 4 patients from the 5-year analysis, nevertheless, was small. An analysis that included the 4 excluded patients in the PT group (using their last scores before implantation of the stimulator) and compared 31 patients in the SCS+PT group with 17 in the PT group still revealed no significant pain reduction in favor of SCS. The same was true for an analysis including all 54 patients with their last available outcomes.

For other disorders, the long-term effectiveness of SCS has been only rarely studied. With regard to angina pectoris, the treatment results were constant during 4.8 years.¹¹ For chronic critical leg ischemia or failed-back surgery syndrome, the follow-up in randomized controlled trials has not exceeded 2 years.^{33,37} There are no indications that this situation will change in the coming years. With regard to SCS for CRPS-I, for example, although only 1 randomized controlled trial is known,²² no less than 3 separate systematic reviews have been published.^{14,28,36} We hope the future will bring new evidence in the form of randomized controlled trials.

Given the 5-year follow-up data, one might question the value of SCS. For several reasons, we remain confident that

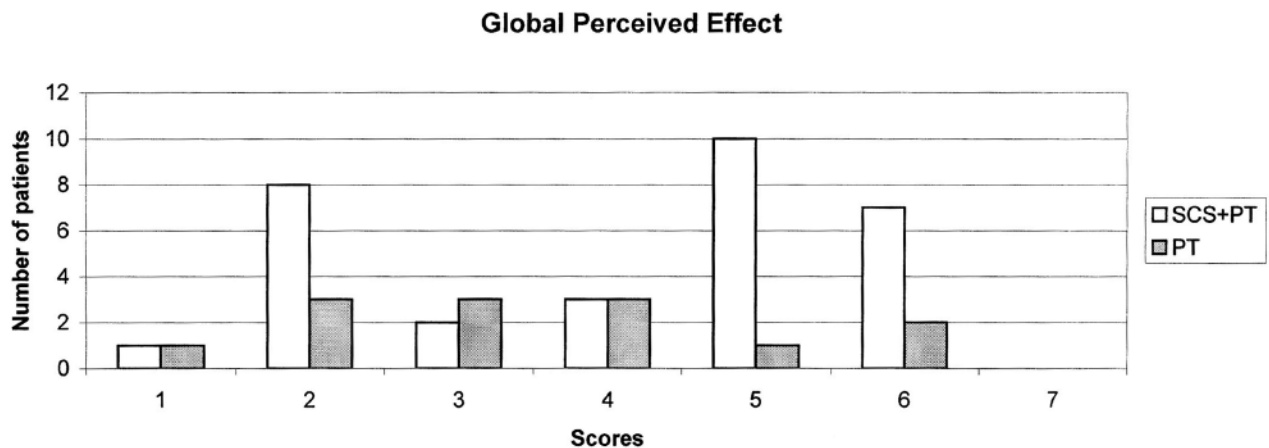


FIG. 3. Bar graph depicting the global perceived effect scores at 2 years in 31 patients in the SCS+PT treatment group and 13 patients in the PT treatment group. 1 = worst ever; 2 = much worse; 3 = worse; 4 = not improved/not worse; 5 = improved; 6 = much improved; 7 = best ever.

TABLE 2
Alternative analyses at the 5-year follow-up*

Characteristic	Analysis w/ Original Group			Analysis w/ Patients in PT Group w/ Implant		
	SCS +PT	PT	p Value	SCS +PT	PT	p Value
no. of patients	36	18		31	17	
mean VAS score (cm)	-1.5 ± 2.3	-0.9 ± 2.8	0.22	-1.7 ± 2.3	-1.1 ± 2.8	0.25
no. of patients w/ ≥ much improved GPE (%)	8 (22)	2 (11)	0.14	7 (23)	2 (12)	0.17
health-related QOL measures (%)						
Nottingham Health Profile						
mobility	6 ± 17	7 ± 25	0.91	7 ± 15	8 ± 26	0.95
pain	-7 ± 26	-3 ± 24	0.55	-7 ± 27	-3 ± 24	0.57
sleep	-15 ± 31	-8 ± 30	0.47	-15 ± 30	-8 ± 31	0.41
energy	-1 ± 44	6 ± 47	0.66	5 ± 43	6 ± 49	0.91
social isolation	4 ± 17	1 ± 17	0.54	4 ± 18	0 ± 18	0.57
emotional reaction	-3 ± 25	1 ± 28	0.63	-2 ± 27	-3 ± 23	0.90
EQ-5D	14 ± 24	13 ± 40	0.90	16 ± 25	15 ± 41	0.94
Self-Rating Depression Scale	-1 ± 8	-2 ± 11	0.59	0 ± 9	-3 ± 10	0.40

* Values represent the means ± SDs.

this treatment is worthwhile in chronic CRPS-I. The study involved chronic cases that had not reacted to standard therapies and whose baseline VAS pain intensity score was 7.0, whereas a score of 5.4 has been demonstrated to equal severe pain.² Pain reduction for 2–3 years in such severe cases must be considered an important achievement. An economic analysis has demonstrated that after 3 years of successful treatment SCS would be cheaper than alternative therapies, and that after 2 years it would be cost-effective.²⁴ The present study indicates that its effectiveness lasts between 2 and 3 years. After 5 years of follow-up, however, there is still high patient satisfaction. According to our predefined criteria, SCS was successful in 11 (35%) of 31 patients; 7 reported much improvement on the global perceived effect scale, and 7 had a 50% decrease in the baseline VAS score. Moreover, of 20 patients with an implanted system at the final follow-up, 18 reported positive effectiveness and 19 indicated a willingness to repeat the treatment for the same result.

Complications are a well-known aspect of SCS; according to earlier studies, such negative events apply mainly to the initiation of treatment.³⁵ Our study confirms these reports. Of all 29 complications that occurred during 5 years of treatment, 21 (72%) took place in the first 2 years. The

annual complication rate in the other 3 years (5%) is much lower than the estimated 30% in the economic analysis. The number of pulse generator replacements in this study confirms the estimated battery life of 5 years according to the economic analysis.

Conclusions

Spinal cord stimulation does not produce a durable and statistically significant improvement in the pain from chronic CRPS-I. Nevertheless, patient satisfaction at the 5-year follow-up remains high.

Disclaimer

None of the authors has a financial interest in the subject under discussion.

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TABLE 3
Complications and pulse generator replacements*

Operation Resulting From Complication	Years 0–2	Year 3	Year 4	Year 5	Total
pulse generator replacement	1	4	4	8	17
repositioning of lead	8	0	1	2	11
pulse generator pocket revision	7	1	0	0	8
replacement lead	2	1	2	1	6
explantation of system	3	0	0	0	3
reimplantation of system	1	0	0	0	1
total	21	2	3	3	29

* Values represent the number of cases; the row and column labeled “total” represent the totals of all but the first row and column. Twenty-nine complications occurred in 10 (42%) of 24 patients, and 13 (54%) of 24 patients underwent 17 pulse generator replacements during the 5 years of follow-up.

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