The Effect of Spinal Cord Stimulation in Patients with Chronic Reflex Sympathetic Dystrophy: Two Years' Follow-up of the Randomized Controlled Trial

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Chronic reflex sympathetic dystrophy is a painful, disabling disorder for which no treatment with proven effect is available. We performed a randomized trial in a 2 to 1 ratio of patients, in which 36 patients were treated with spinal cord stimulation and physical therapy (SCS+PT), and 18 patients received solely PT. Twenty-four SCS+PT patients were given a permanent spinal cord stimulation system after successful test stimulation; the remaining 12 patients received no permanent system. We assessed pain intensity, global perceived effect, functional status, and health-related quality of life. Patients were examined before randomization, before implantation, and also at 1, 3, 6, 12, and 24 months thereafter. At 2 years, three patients were excluded from the analysis. The intention-to-treat analysis showed improvements in the SCS+PT group concerning pain intensity (−2.1 vs 0.0cm; $p < 0.001$) and global perceived effect (43% vs 6% "much improved"; $p = 0.001$). There was no clinically important improvement of functional status. Health-related quality of life improved only in the group receiving spinal cord stimulation. After careful selection and successful test stimulation, spinal cord stimulation results in a long-term pain reduction and health-related quality of life improvement in chronic reflex sympathetic dystrophy.

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Reflex sympathetic dystrophy (RSD) is a pain syndrome of unknown pathophysiology, mostly initiated by a seemingly minor trauma and characterized by ongoing pain, allodynia, functional impairment, abnormal sweating, and abnormal vascular reactivity. All symptoms occur in a distal distribution of a limb, and all are disproportionate to the inciting event. A distinguishing characteristic of RSD is that both pain and other somatosensory abnormalities extend outside the distribution of peripheral nerves, even if the inciting injury had involved a peripheral nerve. Most patients demonstrate only a selection of all possible signs and symptoms associated with RSD, whereas the severity of symptoms is also variable. Only one in five patients is able to fully resume prior activities.[1] The incidence rate has been assumed to be 1 case in every 2,000 accidents.[2] In 1994, the International Association for the Study of Pain proposed stringent diagnostic criteria and introduced the new name: *complex regional pain syndrome type 1*.[3] In this article, we use the more common term *reflex sympathetic dystrophy*.

Many methods have been used to reduce the pain intensity in RSD, for example, conventional pain medication, physical therapy, sympathetic blocks, and transcutaneous electrical nerve stimulation, but all with mainly unfavorable results.[4,5] Spinal cord stimulation (SCS) was introduced in 1967.[6] In this procedure, 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 paresthesiae, a sensation that suppresses the pain. At 6 months' follow-up, this prospective randomized controlled study showed that SCS reduces pain and improves health-related quality of life in chronic RSD, whereas functional status is unchanged.[7] The treatment did not result in long-term effect on detection and pain thresholds for pressure, warmth, or cold.[8] SCS was shown to be both more effective and less costly than the

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standard treatment protocol.[9] Nevertheless, SCS is expensive, a complete system costs at least $8,500, and in some countries far more, and also has drawbacks.[10] Therefore, SCS can genuinely be considered a worthwhile addition to RSD therapy only when prospective studies have proved its effectiveness in the long term.

In this study, results of the prospective randomized controlled study are presented at 2 years' follow-up. We assessed influences of treatment on pain intensity, global perceived effect, functional status, and health-related quality of life.

Patients and Methods

Selection of Patients

Study inclusion was considered for patients meeting the International Association for the Study of Pain criteria for complex regional pain syndrome type 1.[3] Further inclusion criteria were age 18 to 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' physical therapy, sympathetic blocks, transcutaneous electrical nerve stimulation, and medication; and a mean pain intensity of at least 5cm, measured on a visual analog scale from 0 (no pain) to 10cm (very severe pain), according to Jensen and McFarland.[11] Exclusion criteria were presence of Raynaud's disease; presence or previous history of neurological abnormalities not related to RSD; conditions affecting function of diseased or contralateral extremities, other than RSD itself; blood clotting disturbances or anticoagulant drug therapy; cardiac pacemaker use; and a score of 200 or more on the Symptom Check List–90,[12] a standardized psychological test. The study complied with the Declaration of Helsinki and was approved by the medical ethics committee of our institution. All patients gave written informed consent.

Randomization

Patients were assigned through randomization to a group with SCS and a standardized physical therapy program (SCS+PT group), or to a group with the standardized physical therapy program alone (PT group). At the end of the baseline assessment, a concealed randomization procedure was applied with prestratification for upper or lower extremity location of RSD. The patient was assigned, either to SCS+PT or PT, by an uninvolved person who was contacted by telephone and who made use of a computer-generated table of random numbers. The randomization used a 2 to 1 ratio in favor of the SCS+PT group. All patients assigned to SCS+PT underwent test stimulation; those not successfully responding did not receive the SCS system. To estimate the required sample size, pilot study data were used.[10]

Test Stimulation and Implantation Criteria

Test stimulation was performed to assess whether patients respond to SCS positively. The operative procedures of implanting the test and permanent stimulation systems have been previously described.[7]

The decision to implant the permanent SCS system was made when pain intensity during the testing period was at least 50% lower as compared with the original (baseline) visual analog score, or if "much improvement" was reported on a seven-point global perceived effect scale (see below). Patients not meeting these criteria continued the study with physical therapy alone.

Physical Therapy Program

The physical therapy program was offered to all patients in the study and consisted of exercises using a graded activity approach, aimed to improve endurance, mobility, and function of the affected extremity. The program lasted 6 months, with continuation after 6 months being optional. At 2 years, 21 of 51 patients (9 SCS+PT, 12 PT) were still receiving PT. Details of the program also have been described previously.[13]

Data Collection and Follow-up

The patients were assessed before randomization (B = baseline) and on the day before implantation. (Start of treatment of patients not receiving an implant was planned to take place close to start of treatment of implant patients.) Further assessments were made at 1 month (T1), 3 months (T3), 6 months (T6), 12 months (T12), and 24 months (T24) after start of treatment. Outcome measures were grouped into five categories. First, pain was assessed using a visual analog scale, and the McGill pain questionnaire.[14] Second, patients rated global perceived effect on a seven-point scale, indicating: *worst ever*; *much worse*; *worse*; *not improved/not worse*; *improved*; *much improved*; and *best ever*.[15] Third, we assessed functional status of either the upper extremity,[16] or the lower extremity,[17] by measuring the time necessary to perform a subtest in seconds using a stopwatch; the mean of the subtest times providing the final result. Using goniometry, we measured the active range of motion of either both ankles (foot patients), or of both wrists, and the sum of all finger joints (hand patients). One of two parameters was assessed: either grip strength (Jamar dynamometer),[18] or strength of foot dorsiflexors and plantarflexors (handheld myometry).[19] Fourth, health-related quality of life was evaluated using the Nottingham Health Profile,[20] the EuroQol 5D,[21] the Sickness Impact Profile 68,[22] and the Self-rating Depression Scale.[23] These questionnaires had been validated previously and also translated into Dutch.[24–26] Fifth, we listed technical and surgical complications and side effects.

Statistical Analysis

The statistical analysis was conducted according to the "intention-to-treat" principle. For all outcome measures, differences between start of treatment and T24 values for each individual were calculated and compared between both groups using independent samples t tests or, if the results were not normally distributed, nonparametric tests. Fisher's exact tests were used to compare proportions. For global perceived effect (dichotomized in "much improved" or "better" and in "improved" or "worse"), differences between the two groups were calculated. Multivariate regression analysis was performed to assess potential influences of baseline differences in prognostic factors and outcome variables on effect size. Two-tailed p values less than 0.05 were considered to indicate statistical significance.

Results

Between March 1997 and July 1998, we included 54 patients. Randomization was successful, and the two groups were statistically comparable at baseline regarding all prognostic variables and outcome measures (data presented previously).[7,8] The flowchart illustrating the study protocol is presented in Figure 1. Three patients were excluded from the 2-year analysis. Two PT patients were excluded after receiving a spinal cord stimulator. One SCS+PT patient, in whom it had been impossible to place a lead in the epidural space, was excluded subsequent to receiving a special lead after 6 months. Another patient (assigned to PT) refused to undergo any physical test after T0 but was not excluded.

Results Test Stimulation

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

Intention-to-Treat Analysis

Only 2-year (T24) results are reported, but similar changes were obtained at 1 month, 3, 6 and 12 months (Table 1). After 2 years (results at T24 minus results at start of treatment), the mean pain intensity with SCS+PT was reduced by 2.1cm, compared with 0cm with PT ($p < 0.001$; Fig 2). The extent of pain relief was similar for upper and lower extremity patients. Of 35 SCS+PT patients, 15 (43%) reported "much improvement," compared with one (6%) of 16 PT patients ($p = 0.001$; Fig 3). At 2 years, SCS was successful in 20 of 35 patients (57%); 15 reported "much improvement" on the global perceived effect scale, whereas 13 patients showed a 50% decrease of the visual analog score at start of treatment. Observed

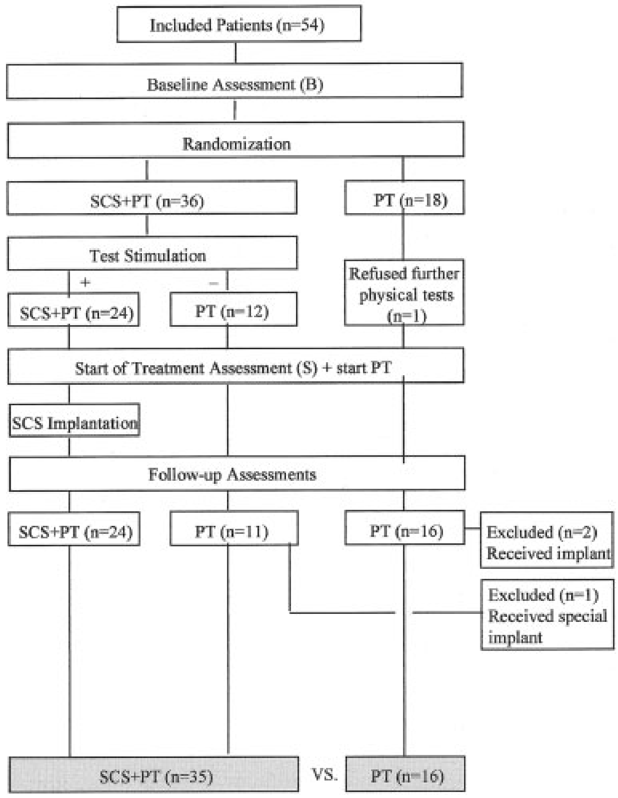

Fig 1. Flowchart illustrating the study protocol and indicating the groups compared in the intention-to-treat analysis.

Table 1. Outcomes of Treatment Evaluated after 2 Years

	Intention-to-Treat Analysis			SCS+PT Subgroups	
Characteristic	SCS + PT (N = 35), ± SD	PT (N = 16), ± SD	p[a]	With Implant (N = 24)	Without Implant (N = 11)
Visual analog pain score (cm)	−2.1 ± 2.8	0 ± 1.5	.001	−3 ± 2.7	0 ± 1.9
Global perceived effect (n, %)[b]	15 (43)	1 (6)	.001	15 (63)	0 (0)
Health-related quality of life (%)	7 ± 20	12 ± 18	.41	12 ± 21	−1 ± 12
Functional score (N)	21	10		15	6
Upper extremities (function) (sec)	2 ± 14	4 ± 21	.78	−3 ± 8	13 ± 19
Upper extremities (strength) (kg)	0 ± 5	−1 ± 3	.54	1 ± 5	−1 ± 5
Upper extremities (ROM–wrist) (degrees)	0 ± 30	−5 ± 37	.73	0 ± 36	0 ± 3
Upper extremities (ROM–hand) (degrees)	−18 ± 181	−119 ± 309	.36	10 ± 176	−89 ± 187
Functional score (N)	14	5		9	5
Lower extremities (function) (sec)	−3 ± 4	−5 ± 5	.48	−1 ± 2	−6 ± 4
Lower extremities (dorsiflexors) (N)	11 ± 27	−8 ± 27	.21	20 ± 29	−6 ± 9
Lower extremities (plantarflexors) (N)	14 ± 43	20 ± 44	.80	21 ± 51	2 ± 23
Lower extremities (ROM–ankle) (degrees)	0 ± 16	13 ± 8	.04	2 ± 20	−3 ± 4

[a]Intention-to-treat analysis (SCS + PT vs PT).
[b]Number (%) of patients reporting at least "much improved" on global perceived effect.

SCS = spinal cord stimulation; PT = physical therapy; SD = standard deviation; ROM = range of motion.

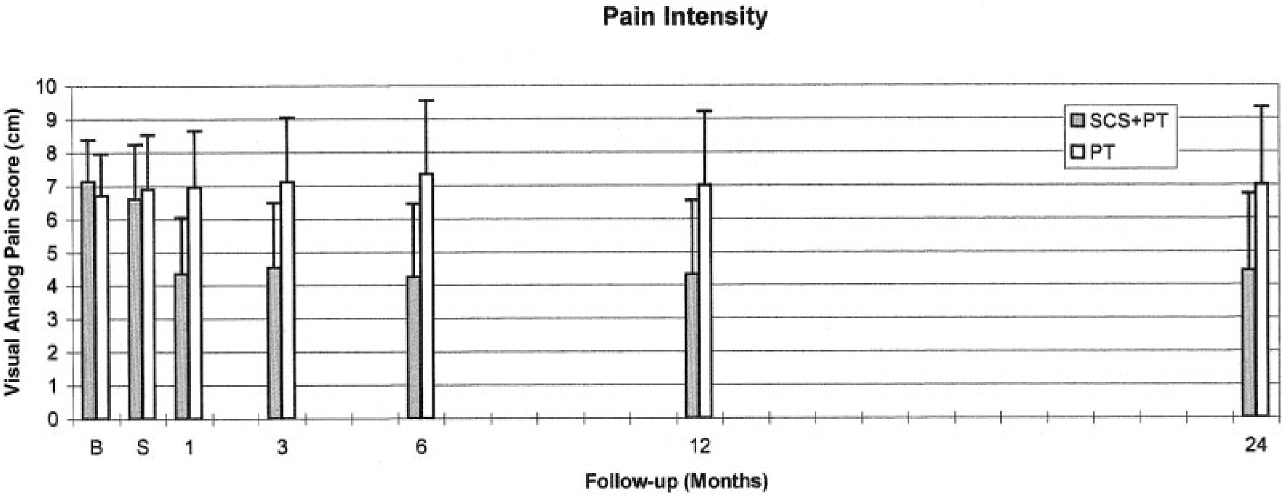

Fig 2. Mean (±SD) visual analog pain scores in centimeters of reflex sympathetic dystrophy patients treated with spinal cord stimulation (SCS) and physical therapy (PT) (filled bars) *or with PT alone* (unfilled bars) *(intention-to-treat analysis). B = baseline; S = start of therapy.*

changes in other pain measures, health-related quality of life, and functional status were not statistically significant between the treatment groups. Multivariate regression analysis demonstrated that no baseline factor except treatment group influenced effect size.

Results in Group Receiving Spinal Cord Stimulation

The mean pain relief of 24 patients with an implanted spinal cord stimulator was 3.0cm, as compared with 0cm change among 16 patients receiving physical therapy ($p < 0.001$; see Table 1). Fifteen of 24 patients (63%) with SCS reported "much improvement," compared with 1 of 16 patients (6%) receiving physical therapy ($p < 0.001$). SCS also improved the pain rating index of McGill Pain Questionnaire ($p = 0.02$) and the health-related quality-of-life dimension "Pain" (Nottingham Health Profile) for both upper ($p = 0.02$) and lower ($p = 0.008$) extremities (data not in table). The treatment did not influence functional status.

In total, 9 of 24 patients (38%) suffered 22 complications needing operation during the 2 years after implantation (Table 2). The most frequent complications were electrode displacement and pain from the pulse generator pocket. Two patients underwent permanent removal of the system on the grounds of recurrent rejection and relapsing ulcerative colitis subscribed to the system, respectively.[27,28] Side effects were reported by all 22 patients who still had an implanted system at 2 years.

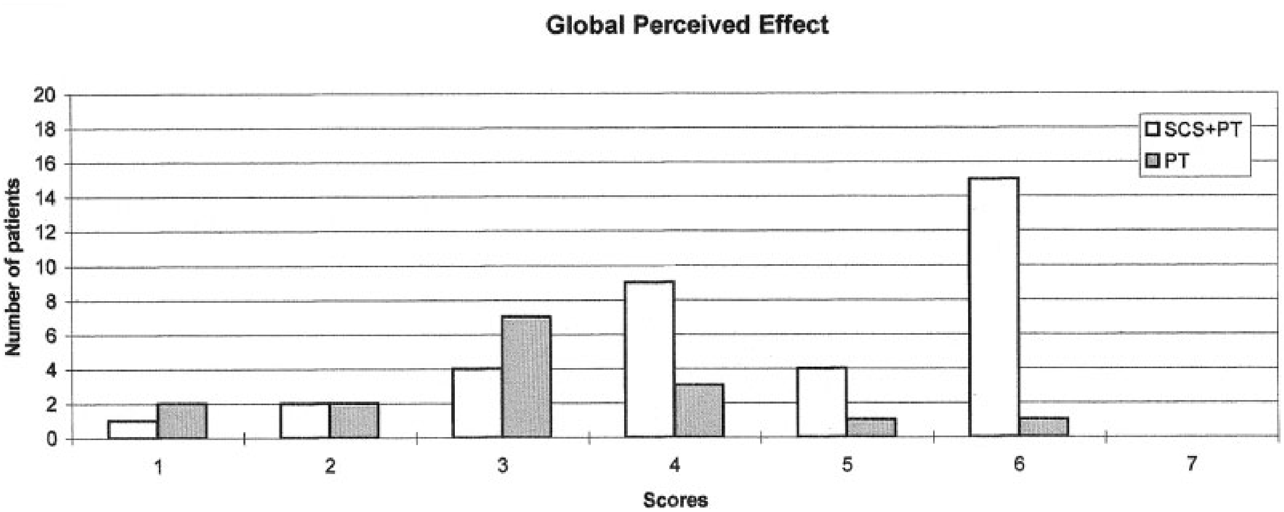

Fig 3. Global perceived effect scores at 2 years in number of patients. (unfilled bars) *Spinal cord stimulation (SCS) and physical therapy (PT; n = 35).* (filled bars) *Physical therapy alone (n = 16). 1 = worst ever; 2 = much worse; 3 = worse; 4 = not improved/not worse; 5 = improved; 6 = much improved; 7 = best ever.*

Table 2. Complications and Side Effects

	Year 1	Year 2	Total
Complication (reoperation)			
Repositioning of lead	8	0	8
Revision pulse generator pocket	7	0	7
Replacement lead	1	1	2
Explantation system	1	2	3
Reimplantation system	1	0	1
Replacement pulse generator	0	1	1
Side effect			Total
Change of amplitude by bodily movements			19
Paresthesiae in other body parts			13
Pain/irritation from extension lead or plug			11
Pain/irritation from pulse generator			10
More pain in other body parts			7
Disturbed urination			4
Movements or cramps resulting from elevated amplitude			3

Complications occurred in nine patients during 2 years of follow-up. All patients reported side effects.

A change in stimulation amplitude resulting from bodily movements was the most frequently reported problem.

Discussion

Our study, the first randomized controlled trial on SCS for RSD to our knowledge, provides evidence that SCS reduces pain intensity of chronic RSD patients during 2 years of follow-up. In general, very few treatments can influence symptoms caused by RSD,[4,5] and our chronic cases, in particular, had not even exhibited any reaction at all to any of the standard therapies. Their mean baseline visual analog pain intensity score was 7.0, in which a score of 5.4 has been demonstrated to equal severe pain.[29] A treatment capable of influencing such severe cases must be considered a very significant improvement.

Success in treatment is dependent on strict inclusion criteria,[30] excluded psychopathology,[31,32] and full coverage of the painful area by paraesthesiae.[33] Our study shows that when these criteria are fulfilled in RSD patients, the sole effect of SCS is the alleviation of pain. Chronic RSD generates extreme pain and disability, which has a great impact on the lives of patients and their families.[34] Because RSD does not end where SCS starts, future candidates should be clearly informed that although the treatment effectively reduces pain in approximately 60% of patients, it has no influence on allodynia, hypoesthesia, or function.[8]

During 2 years of follow-up, complications occurred in 38% of patients. Because SCS is a lifelong therapy, it is of interest, both clinically and financially, to realize that the frequency of complications shows a marked reduction after the first year; subsequently, the only significant items of recurrent expenditure are pulse generator replacements.

Side effects were reported by all patients with an implant. Most patients dislike the fact that the electrode relocates vis-à-vis the dorsal column whenever there is spinal movement, resulting in troublesome amplitude changes. Pain or irritation from subcutaneous system parts is also frequently reported. To the best of our knowledge, side effects of SCS have not been reported previously. However, in our opinion, it is crucial to assess these, because side effects are an inherent problem with the treatment and one that is effectively impossible to solve.

We conclude that after careful selection and successful test stimulation SCS is safe and has long-term effectiveness in reducing pain. There is ample evidence to show that its application leads to a better health-related quality of life in patients with chronic RSD.

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