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SPINAL CORD STIMULATION IN PATIENTS WITH CHRONIC REFLEX SYMPATHETIC DYSTROPHY

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ABSTRACT

Background Chronic reflex sympathetic dystrophy (also called the complex regional pain syndrome) is a painful, disabling disorder for which there is no proven treatment. In observational studies, spinal cord stimulation has reduced the pain associated with the disorder.

Methods We performed a randomized trial involving patients who had had reflex sympathetic dystrophy for at least six months. Thirty-six patients were assigned to receive treatment with spinal cord stimulation plus physical therapy, and 18 were assigned to receive physical therapy alone. The spinal cord stimulator was implanted only if a test stimulation was successful. We assessed the intensity of pain (on a visual-analogue scale from 0 cm [no pain] to 10 cm [very severe pain]), the global perceived effect (on a scale from 1 [worst ever] to 7 [best ever]), functional status, and the health-related quality of life.

Results The test stimulation of the spinal cord was successful in 24 patients; the other 12 patients did not receive implanted stimulators. In an intention-to-treat analysis, the group assigned to receive spinal cord stimulation plus physical therapy had a mean reduction of 2.4 cm in the intensity of pain at six months, as compared with an increase of 0.2 cm in the group assigned to receive physical therapy alone ($P<0.001$ for the comparison between the two groups). In addition, the proportion of patients with a score of 6 ("much improved") for the global perceived effect was much higher in the spinal cord stimulation group than in the control group (39 percent vs. 6 percent, $P=0.01$). There was no clinically important improvement in functional status. The health-related quality of life improved only in the 24 patients who actually underwent implantation of a spinal cord stimulator. Six of the 24 patients had complications that required additional procedures, including removal of the device in 1 patient.

Conclusions In carefully selected patients with chronic reflex sympathetic dystrophy, electrical stimulation of the spinal cord can reduce pain and improve health-related quality of life. (N Engl J Med 2000;343:618-24.)

REFLEX sympathetic dystrophy is a pain syndrome of unknown pathophysiology that affects the foot or the hand. The disorder may be caused by trauma or surgery or may develop spontaneously. Excruciating, burning pain and functional impairment are the most disabling characteristics of the syndrome; other symptoms and signs are listed in Table 1. Only one in five affected patients is able to return to a normal level of functioning.[1] Since many different diagnostic criteria have been used, the exact incidence of reflex sympathetic dystrophy is unknown, but it has been estimated to occur in approximately 1 of every 2000 traumatic events.[2] In 1994, the International Association for the Study of Pain proposed stringent diagnostic criteria and named the disorder the "complex regional pain syndrome type 1."[3] We use the more common term, "reflex sympathetic dystrophy."

Conventional pain medication, physical therapy, sympathetic blocks, and transcutaneous electrical stimulation of nerves have all been used to reduce the intensity of pain caused by reflex sympathetic dystrophy, but with generally unfavorable results.[4,5] Several retrospective analyses have shown that stimulation of the spinal cord, a treatment introduced in 1967,[6] controls pain in patients with reflex sympathetic dystrophy.[7-10] 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 induces paresthesias, a sensation that suppresses the pain. The current is supplied by a pulse generator positioned subcutaneously in the anterior abdominal wall and connected to the electrode by an extension lead. Patients can reduce or increase the intensity of the current by means of a device that uses radio-frequency transmission. Because spinal cord stimulation is expensive (a complete system costs at least $8,500, and the cost is much higher in some countries) and has drawbacks,[10] there is a need for prospective studies to confirm its effectiveness.

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TABLE 1. DIAGNOSTIC CRITERIA FOR REFLEX SYMPATHETIC DYSTROPHY IN THE STUDY.*

Absolute criteria
Pain
Impaired function†
Symptoms beyond the area of trauma†
Cold, warm, or intermittently cold and warm feeling in the affected area
Relative criteria
Edema
Increased nail growth
Increased hair growth
Hyperhidrosis
Abnormal skin color
Hypoesthesia
Hyperalgesia
Mechanical or thermal allodynia or both
Patchy demineralization of bone

*All the absolute criteria, together with at least three of the relative criteria, were required for the diagnosis of reflex sympathetic dystrophy.

†This item is not included in the criteria of the International Association for the Study of Pain.

We performed a prospective, randomized, controlled study to determine whether treatment of chronic reflex sympathetic dystrophy with spinal cord stimulation and physical therapy is more effective than treatment with physical therapy alone. We assessed the influence of treatment on the intensity of pain, the global perceived effect, functional status, and the health-related quality of life.

METHODS

Patients

Patients were eligible for the study if they were 18 to 65 years old and met the diagnostic criteria for reflex sympathetic dystrophy established by the International Association for the Study of Pain,[3] with impaired function and symptoms beyond the area of trauma (Table 1). Additional criteria for enrollment included disease that was clinically restricted to one hand or foot and affected the entire hand or foot, that had lasted for at least six months, and that did not have a sustained response to standard therapy (six months of physical therapy, sympathetic blockade, transcutaneous electrical nerve stimulation, and pain medication), with a mean pain intensity of at least 5 cm on a visual-analogue scale from 0 cm (no pain) to 10 cm (very severe pain).[11]

Exclusion criteria were the presence of Raynaud's disease, current or previous neurologic abnormalities unrelated to reflex sympathetic dystrophy, another condition affecting the function of the diseased or contralateral extremity, a blood-clotting disorder or use of an anticoagulant drug, and use of a cardiac pacemaker.

All eligible patients completed the 90-item Symptom Check List,[12] a standardized questionnaire that measures psychological distress. On this scale, scores can range from 90 to 450, with higher scores indicating more psychological distress. Patients who had a score of 200 or more underwent a full examination by a psychologist to rule out substance abuse and major psychiatric disorders and to address issues of possible secondary gain from the treatment of illness. Patients who were considered, on the basis of the examination, to have serious psychiatric disorders were excluded.

The study complied with the provisions of the Declaration of Helsinki with regard to research involving human subjects and was approved by the medical ethics committee of Maastricht University Hospital in Maastricht, the Netherlands. All patients gave written informed consent.

Randomization

After undergoing a base-line assessment, patients were randomly assigned in a 2:1 ratio to receive treatment with spinal cord stimulation and a standardized physical-therapy program or with the standardized physical-therapy program alone. A computer-generated table of random numbers was used to make the treatment assignments, with stratification according to the location of the reflex sympathetic dystrophy (hand or foot). The assignments were made by a research assistant and were concealed from the study investigators.

Test Stimulation and Criteria for Implantation

Spinal cord stimulation was tested to determine whether there was a positive response to it. All patients assigned to receive the spinal cord implant underwent a test stimulation; those who did not have a response did not receive the implant. After the prophylactic administration of an antibiotic agent (1500 mg of cefuroxime given intravenously), the patient was placed in a prone position, and the epidural space was entered with a Tuohy needle. With the use of direct fluoroscopy, a temporary electrode (model 3861, Medtronic, Minneapolis) was advanced through the needle in the posterior epidural space until the tip was at the required level (generally C4 if the hand was affected and T12 if the foot was affected). The electrode was then connected to an external stimulator (model 3625, Medtronic) and positioned so that, on stimulation, the patient reported paresthesias over the entire area of pain. The needle was then withdrawn, and the electrode was stitched to the skin and connected to the external stimulator. There was a home-testing period of at least seven days, which is consistent with conventional practice,[13,14] during which the patients were encouraged to perform their normal daily activities. After the testing period, the temporary lead was removed.

The spinal cord stimulator was implanted if the visual-analogue score for the intensity of pain during the last four days of the testing period was at least 50 percent lower than the score before randomization, or if there was a score of at least 6 ("much improved") on a seven-point scale for the global perceived effect of treatment. Patients who did not meet these criteria were treated with physical therapy alone.

Implantation of the Spinal Cord Stimulator System

After the prophylactic administration of cefuroxime (1500 mg given intravenously), the patient was placed in the prone position and a 5-cm vertical midline incision was made in the skin overlying the thoracic spine (if the hand was affected) or the lumbar spine (if the foot was affected). An electrode (model 3487A, Medtronic) was implanted in a fashion similar to the implantation of the temporary lead and was fixed with special clips. The patient was then placed in a lateral position, and a sedative was administered (1 mg of propofol per kilogram of body weight). A pulse generator (Itrel III, model 7425, Medtronic) was implanted subcutaneously in the left lower anterior abdominal wall and connected to the electrode by a tunneled extension lead (model 7495-51/66, Medtronic). After the skin had been closed, the pulse generator was activated (rate, 85 Hz; pulse width, 210 μsec) with the use of a console programmer (model 7432, Medtronic). The patient could control the intensity of stimulation by adjusting the amplitude from 0 to 10 V with a programmer (model 7434-NL, Medtronic). The patient remained in the hospital for 24 hours after the implantation, during which time two doses of cefuroxime (750 mg each) were given intravenously. If no change in the position of the electrode was evident on an x-ray film obtained the following day, the patient was discharged.

Physical Therapy

Physical therapy, which both groups of patients received, consisted of a standardized program of graded exercises designed to improve the strength, mobility, and function of the affected hand or foot. Pain during the exercises was considered acceptable, but if it had not returned to the presession level within 24 hours, the intensity of the exercises was reduced. Physical therapy was administered for 30 minutes twice a week, with a minimum of two days between sessions. The total duration of the physical therapy was six months, starting after the second assessment. To ensure standardization, selected physical therapists were trained to provide the program of exercises. The coordinating physical therapist from our institution visited the other therapists regularly to make sure the treatment was uniform.

Data Collection and Follow-up

Outcome measures were assessed before randomization and on the day before implantation for patients in the group assigned to stimulation plus physical therapy and before the start of physical therapy for the patients in the physical-therapy group. Additional assessments were performed one month, three months, and six months after the initiation of treatment. There were five categories of outcome measures. First, pain was assessed with the use of a visual-analogue scale[14] and the McGill Pain Questionnaire, which includes a score for the number of words chosen and a pain-rating index.[15] On the first part of this scale, scores can range from 0 to 20, with higher scores indicating more pain. On the second part, scores can range from 0 to 63, with higher scores indicating more pain. Second, patients rated the global perceived effect on a seven-point scale (1, worst ever; 2, much worse; 3, worse; 4, not improved and not worse; 5, improved; 6, much improved; and 7, best ever).[16] Third, we measured functional status, using the test of Jebsen et al.[17] for the hand and a specially devised test for the foot.[18] For both procedures, the time necessary to perform a subtest is measured in seconds with the use of a stopwatch; the mean of the subtest times is the final result. Using goniometry, we measured the range of motion of both ankles (in the case of patients with affected feet) or of both wrists and all finger joints (in the case of patients with affected hands). A Jamar dynamometer was used to measure grip strength,[19] and a handheld myometer was used to measure the strength of foot dorsiflexion and plantar flexion.[20] Fourth, the health-related quality of life was evaluated with the use of the Nottingham Health Profile,[21] the Euroqol 5D,[22] a short version of the Sickness Impact Profile,[23] and the Self-Rating Depression Scale.[24] These questionnaires had previously been validated and translated into Dutch.[25-27] Finally, we documented complications of spinal cord stimulation.

Statistical Analysis

Data from a pilot study were used to estimate the required sample size.[10] The prespecified definition of pain relief was a reduction of at least 3.5 cm on the visual-analogue scale at six months in the group of patients who received implanted spinal cord stimulators. Since we assumed that 33 percent of the patients who were assigned to receive the implant would not have a response to the test stimulation (zero improvement), the criterion for pain relief in this group was a reduction of at least 2.3 cm ($[0.66\times3.5]+[0.33\times0]$). Using the standard deviation from the pilot study (2.34 cm), we calculated that 51 patients (34 in the group assigned to stimulation plus physical therapy and 17 in the physical-therapy group) would be needed to provide the study with a power of 90 percent to detect a 2.3-cm difference between the groups at a two-tailed alpha level of 0.05.

The statistical analysis was carried out according to the intention-to-treat principle. For all outcome measures, differences between the values after randomization but before the start of treatment and the values at six months were calculated for each patient, and the values in the two groups were compared with the use of t-tests for independent samples or with the use of nonparametric tests if the results were not normally distributed. Fisher's exact test was used to compare proportions. For the global perceived effect (dichotomized as a score of <6 or ≥ 6), there are no pretreatment data; consequently, only differences between the two groups were calculated. Multivariate regression analysis was performed to assess the potential influences of base-line differences between the groups and outcome variables on the size of the treatment effect. Two-tailed P values of less than 0.05 were considered to indicate statistical significance.

Table 2. Base-Line Characteristics of the Patients According to the Assigned Treatment.*

Characteristic	Spinal Cord Stimulation plus Physical Therapy (N=36)	Physical Therapy Alone (N=18)
Age — yr	40±12	35±8
Sex — no. (%)		
Male	14 (39)	3 (17)
Female	22 (61)	15 (83)
Duration of disorder — mo	40±28	34±22
Location — no. (%)		
Hand	22 (61)	11 (61)
Foot	14 (39)	7 (39)
SCL-90 score†	143±28	146±32
Pain score on visual-analogue scale — cm‡	7.1±1.5	6.7±1.2
Health-related quality of life — %§	47±19	42±19

*Plus–minus values are means ±SD.

†Scores on the 90-item Symptom Check List (SCL-90) are on a scale of 90 to 450, with higher scores indicating greater psychological distress.

‡Patients indicated the intensity of pain on a visual-analogue scale from 0 to 10 cm, with higher values indicating more severe pain.

§To measure the health-related quality of life, the patients used a visual-analogue scale on which 0 indicates death and 100 indicates perfect health.

RESULTS

Between March 1997 and July 1998, 110 patients were referred to our department as potential candidates for the study. We enrolled 54 of these patients; 36 were assigned to receive spinal cord stimulation and physical therapy, and 18 were assigned to receive physical therapy alone. Of the 56 patients who were excluded, 40 were not eligible and 16 declined to participate. Eight of 77 patients who completed the Symptom Check List had a score of 200 or higher; 1 of the 8 was enrolled in the study after undergoing a psychological examination.

The reflex sympathetic dystrophy was precipitated by trauma in 26 of the enrolled patients and by surgery in 24, and it developed spontaneously in 4. All patients had severe pain and functional impairment that made them unable to work. Of the 33 patients with an affected hand, 20 were unable to use the hand for any daily activity; 13 used a splint. Of the 21 patients with an affected foot, 10 used a wheelchair and 8 used crutches. Of the 54 enrolled patients, 1 (assigned to the physical-therapy group) declined any physical tests after the initial assessment. There were no significant differences in base-line characteristics between the two treatment groups (Table 2).

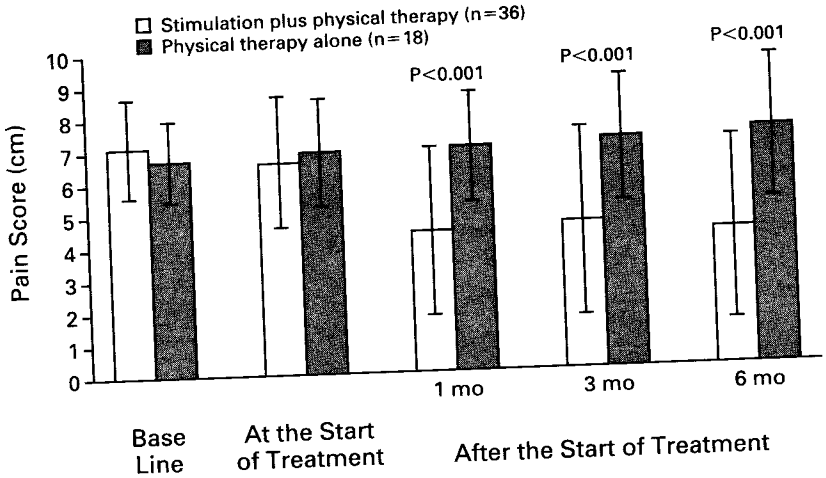

Figure 1. Mean (±SD) Scores for Pain Intensity in Patients with Reflex Sympathetic Dystrophy Who Were Assigned to Spinal Cord Stimulation plus Physical Therapy or to Physical Therapy Alone.
The intensity of pain was measured on a visual-analogue scale from 0 cm (no pain) to 10 cm (very severe pain). Data are from the intention-to-treat analysis.

Results of Test Stimulation

Test stimulation was complicated by a dural puncture in four patients, causing a temporary headache in two of the four. In one patient, it was impossible to enter the epidural space with the Tuohy needle; this patient did not receive an implant. Test stimulation was successful in 24 of the 36 patients assigned to undergo implantation (67 percent): all 24 had a score of 6 (much improved) for the global perceived effect, and 19 had a visual-analogue score that was at least 50 percent lower than the base-line score.

Results at Six Months

Except for the data on functional status, the results at one month and at three months were similar to the results at six months. Therefore, only the results at six months are reported. The mean score on the visual-analogue scale of pain in the group assigned to stimulation plus physical therapy was reduced by 2.4 cm at six months, whereas the score was increased by 0.2 cm in the physical-therapy group ($P<0.001$) (Fig. 1 and Table 3). The extent of pain relief was similar for patients with an affected hand and those with an affected foot. Of the 36 patients assigned to receive stimulation and physical therapy, 14 (39 percent) had a score of 6 for the global perceived effect, as compared with 1 of the 18 patients (6 percent) assigned to receive physical therapy alone ($P=0.01$) (Fig. 2). Spinal cord stimulation was successful in 20 of 36 patients (56 percent); 14 had a score of 6 for the global perceived effect, and 18 had a visual-analogue score that was at least 50 percent lower than the base-line score. Multivariate regression analysis showed that no base-line factor except the treatment assignment influenced the size of the effect. The changes in other measures of pain and measures of functional status and health-related quality of life at six months did not differ significantly between the treatment groups.

Among the 24 patients who were actually treated with spinal cord stimulation, the score on the visual-analogue scale decreased by a mean of 3.6 cm, whereas the score increased by a mean of 0.2 cm among the 18 patients who received physical therapy ($P<0.001$) (Table 3). Fourteen of the 24 patients who received spinal cord stimulation (58 percent) had a score of 6 (much improved) for the global perceived effect, as compared with 1 of 18 patients (6 percent) who received physical therapy alone ($P<0.001$). As compared with physical therapy alone, spinal cord stimulation also resulted in significant improvements in the pain-rating index ($P=0.02$) and the health-related quality of life (the pain component of the Nottingham Health Profile) for both patients with an affected hand ($P=0.02$) and those with an affected foot ($P=0.008$). The treatment did not result in any functional improvement.

Complications

Implantation of the permanent spinal cord stimulation system was complicated by a dural puncture in two patients (with headache in one). Six of the 24 patients treated with spinal cord stimulation (25 percent) had a total of 11 other complications during the six months after implantation. Four patients had long-term complications. One of the four patients had clinical signs of infection, which required antibiotics and removal of the implant. After the signs

Table 3. Outcomes at Six Months According to Actual Treatment and Assigned Treatment.*

Outcome	Assigned to Receive Implant plus Physical Therapy			Assigned to Receive Physical Therapy Alone (N=18)	P Value†
	Received Implant (N=24)	Did Not Receive Implant (N=12)	Total (N=36)		
Change in pain score on visual-analogue scale — cm	−3.6±2.0	0.2±0.9	−2.4±2.5	0.2±1.6	<0.001
Improvement in global perceived effect — no. (%)‡	14 (58)	0	14 (39)	1 (6)	0.01
Change in functional status — hand					
No. of patients	15	7	22	11	
Function — sec§	0±6	6±14	2±10	−1±5	0.21
Strength — kg	5±9	−1±4	3±8	1±3	0.44
Range of motion					
Wrist — degrees	7±35	−7±15	2±30	−3±30	0.61
All fingers — degrees	76±160	−92±179	23±181	−39±190	0.38
Change in functional status — foot					
No. of patients	9	5	14	6	
Function — sec§	−1±2	−1±5	−1±3	−1±3	0.96
Dorsiflexion — N	24±31	−4±8	14±28	3±4	0.16
Plantar flexion — N	38±76	−4±5	23±63	40±51	0.54
Range of motion of ankle — degrees	18±19	−2±2	11±18	8±10	0.71
Change in health-related quality of life — %	11±23	−5±15	6±22	3±18	0.58

*Plus–minus values are means ±SD.

†P values are for the comparison between the group assigned to receive an implant plus physical therapy and the group assigned to receive physical therapy alone.

‡Improvement denotes a score of at least 6 (much improved).

§The results of tests of hand and foot function are given as the time required to perform the test.

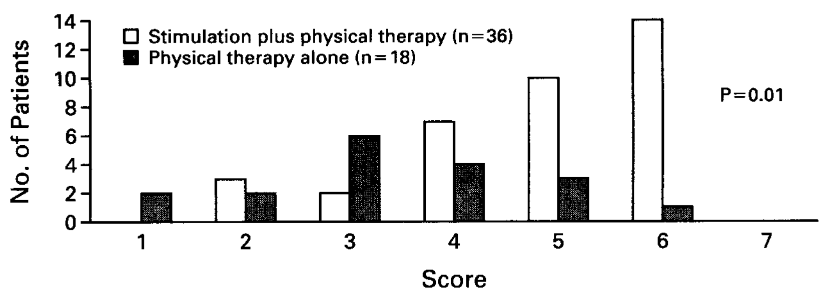

Figure 2. Scores for the Global Perceived Effect at Six Months According to the Assigned Treatment. A score of 1 denotes worst ever, 2 much worse, 3 worse, 4 not improved and not worse, 5 improved, 6 much improved, and 7 best ever. Data are from the intention-to-treat analysis.

of infection, which was not confirmed by bacteriologic culture, had resolved, the patient underwent reimplantation. In two other patients, a painful pulse-generator pocket was modified, and in one patient, a defective lead was replaced. Complications related to unsatisfactory positioning of the electrode occurred in five patients. A single operative procedure performed to reposition the electrode was successful in four of the five patients; correct positioning required three procedures in the fifth patient.

DISCUSSION

We conducted a randomized, controlled trial of spinal cord stimulation for reflex sympathetic dystrophy, which is also known as the complex regional pain syndrome. The results show that spinal cord stimulation reduces the intensity of pain caused by this disorder in patients in whom all conventional treatments have failed.

Several studies have shown that spinal cord stimulation is safe and effective for the treatment of chronic pain.[28-30] Complications, generally minor, have been reported in 20 to 75 percent of patients.[31] In our study, there were complications in 6 of 24 patients (25 percent) during a period of six months after implantation. In most cases, complications were related to the fact that the position of the electrode was unsatisfactory.

The success of spinal cord stimulation depends on the use of strict criteria for the selection of patients,[32] with the exclusion of those who have psychiatric disorders,[33,34] and on full coverage of the painful area by paresthesias.[35] Because of the paresthesias that accompany stimulation, studies of spinal cord stimulation cannot be blinded, but it is unlikely that our results reflected a placebo response, for two reasons. First, the results at one month and at six months were similar, and a sustained benefit of stimulation has previously been reported.[30] Second, pain relief is not achieved unless the entire painful area is covered by paresthesias, and the pain recurs when the electrode is moved.[30]

During the period when the patients were aware of the treatment assignment and of the results of the test stimulation but actual treatment had not yet been initiated, there was a significant improvement in the scores for health-related quality of life and pain intensity in the group assigned to receive spinal cord stimulation plus physical therapy, as compared with the scores in the physical-therapy group.[36] To evaluate better the true outcome of treatment, we therefore compared the values at six months with the values during the period after randomization but before the start of treatment, instead of with the values before randomization.

Because of the risks and high costs of spinal cord stimulation, the treatment is reserved for severely disabled patients. Our study was restricted to patients with reflex sympathetic dystrophy who had experienced severe pain that was unresponsive to conventional treatments for at least six months. Therefore, the results of our study cannot be applied to all patients with reflex sympathetic dystrophy. The intention-to-treat analysis showed significant improvements in the scores for intensity of pain and the global perceived effect in the group of patients assigned to receive spinal cord stimulation, even though one third of these patients had not had a response to the test stimulation and had no stimulator implanted. Among the patients who did have a response to the test stimulation, the treatment resulted in improvements in the scores for pain intensity, the pain-rating index, the global perceived effect, and the health-related quality of life.

Functional status did not improve in either group of patients. At base line, most patients were severely disabled, and many were dependent on the use of a wheelchair or a splint. With such severe disability, contractures and muscle atrophy may be so far advanced that functional improvement is unlikely. However, we also found no evidence that the use of spinal cord stimulation early in the course of reflex sympathetic dystrophy can improve function, since there was no correlation between the duration of the disease or functional status at base line and functional status at six months. Spinal cord stimulation treats pain but not the disease itself, and consequently, a reduction in pain is not accompanied by an improvement in function.

Spinal cord stimulation led to an 11 percent improvement in the overall score for the health-related quality of life. This effect was derived chiefly from the alleviation of pain. In our study population, pain was the primary source of distress. Therefore, despite the lack of effect of spinal cord stimulation on other aspects of the health-related quality of life, the treatment results in an important overall improvement. Whether this improvement justifies the high costs must be determined by a cost-effectiveness analysis.

We conclude that with careful selection of patients and successful test stimulation, spinal cord stimulation is safe, reduces pain, and improves the health-related quality of life in patients with chronic reflex sympathetic dystrophy.

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New Treatments for Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy was first described by Mitchell, in 1864.[1] It has been difficult for clinicians to diagnose this disorder because it has many variations, often follows minor injury, and evolves and spreads over time.[2,3] There are five main types of symptoms: pain, autonomic dysfunction, edema, a movement disorder, and dystrophy and atrophy. A new classification of this disorder and a new name, the complex regional pain syndrome, have been proposed in an effort to describe its clinical features more accurately and avoid the implications of the name "reflex sympathetic dystrophy." The role of the sympathetic nervous system in many aspects of the illness is not clear, and dystrophy may not occur in all patients. In complex regional pain syndrome type 1, all the features of reflex sympathetic dystrophy are present, with no definable nerve injury; in type 2 (formerly called causalgia), a definable nerve injury is present.[4]

In the early stages of reflex sympathetic dystrophy, the pain is more severe than would be expected for the degree of tissue damage, and the pain spreads progressively from a nerve or dermatomal distribution to a regional distribution. The pain is often characterized as a constant burning from its onset, is diffuse both superficially and deeply, and has a palmar or plantar predominance. Spontaneous pain is frequent, and most patients initially have hyperalgesia (more pain than that which would be expected from a painful stimulus) and allodynia (pain from an innocuous stimulus). Later in the course of the disorder, there is hyperpathia (an increased threshold to pain that, once exceeded, results in pain that reaches its maximal intensity too quickly and is not stimulus-bound). The nails become ridged, thickened, and brittle; the hair darkens and grows rapidly in the affected area. In the distal portion of the affected extremity, there may be increased or decreased skin temperature, hyperhidrosis, livedo reticularis, dusky cyanosis, delayed capillary refill, and diffuse mottling. Spasms, increased reflexes, and weakness are common. In approximately 20 percent of patients, the affected area is initially painful, warm, and red.

As the illness evolves, the constant burning pain, hyperalgesia, and allodynia intensify and may be accompanied by disruption of sleep, anxiety, and depression. The skin may show brawny edema and is usually hyperhidrotic, cool, cyanotic, and mottled. Loss of hair occurs in areas where its growth was previously stimulated. The bones may undergo cystic and subchondral erosion, as well as diffuse osteoporosis (Sudeck's atrophy).

After several years, the illness is characterized by ever-increasing pain, dystrophy, and atrophy. A small percentage of patients report pain throughout the body. In some patients, the disorder remains stable for years, whereas in others it progresses rapidly. The symptom complex may be dissociated in any stage of the illness — for example, there may be pain in one hand and autonomic dysfunction in the other.

In its early stages, reflex sympathetic dystrophy may be maintained by sympathetic neural activity, but with time it becomes independent of sympathetic activity. There is no evidence that affected patients have a personality disorder, but the severity of the pain and the disruption of the patient's life can lead to depression and anxiety.[5] There is some evidence of a genetic predisposition.

In general, reflex sympathetic dystrophy is caused by direct trauma to soft tissue, bone, or a major nerve or plexus in which nociceptive terminals are injured. Studies in animals have shown that allodynia, thermal hyperalgesia, sympathetic maintenance (in which case sympathetic blockade relieves the pain), dystonia, and altered pain behavior are consistent with lowered pain thresholds.[6]

The pain in patients with reflex sympathetic dystrophy is consistent with the mechanisms of activity-dependent plasticity in which nociceptive terminals innervating the damaged area and the central pain-projecting nerves of the dorsal horn undergo changes in physiologic function as the result of a complicated series of intracellular enzyme cascades, receptor modifications, and novel gene expression. This modulation results in the central sensitization that amplifies the pain response of the central nervous system.[7] The edema that often accompanies reflex sympathetic dystrophy may be a manifestation of neurogenic inflammation in which C fibers that innervate blood vessels in the affected area release vasoactive neuropeptides that cause vasodilatation and increased permeability, with consequent transudation of fluid and protein.[8]

Recent clinical studies of autonomic function in patients with reflex sympathetic dystrophy have demonstrated a profound abnormality of respiratory and thermoregulatory sympathetic neurogenic reflexes early in the course of the disorder that clears with clinical recovery, as well as abnormalities in sweat output and skin temperature at rest and in microcirculatory responses to both peripheral and central autonomic stimuli. The clinical findings indicate that patients with reflex sympathetic dystrophy have autonomic dysfunction within the central nervous system.[9]

The movement disorder that is characteristic of reflex sympathetic dystrophy has five main components: an inability to initiate movement, weakness, tremor, muscle spasms, and dystonia.[10,11] These motor manifestations may precede the pain, may appear suddenly, and may occur on the contralateral side of the body. Rarely, both the arms and the legs may be affected. In the upper extremity, the dystonia starts with flexion and contraction of the fourth and fifth

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fingers of the hand and evolves into adduction and flexion of the arm and wrist. In the lower extremity, the foot is inverted, with plantar flexion. A few patients have dystonic extensor postures. The process is devastating and renders the extremity nonfunctional. These motor manifestations may be alleviated by sympathetic blockade but only in the early stages of reflex sympathetic dystrophy. The mechanisms that cause the dystonia are unclear. There may be enhancement of nociceptive flexor withdrawal reflexes and decreased presynaptic inhibition of nociceptive afferents by γ-aminobutyric acid–employing (GABAergic) inhibitory neurons.[12,13]

Two fine clinical studies of novel treatments for the pain and dystonia of reflex sympathetic dystrophy are reported in this issue of the *Journal.* Kemler and colleagues describe a randomized trial of spinal cord stimulation.[14] In an intention-to-treat analysis, the patients assigned to receive this treatment had greater improvement in scores for the intensity of pain and the perceived effect of treatment than did the patients assigned to the control group. The health-related quality of life improved only in the patients who actually underwent spinal cord stimulation. Unfortunately, the patients had no functional improvement as a result of this treatment. Kemler et al. note that complications occur in 20 to 75 percent of patients who undergo spinal cord stimulation. In most patients, the complications are associated with unsatisfactory positioning of the electrode. The authors make a case for total coverage of the affected area with induced paresthesias in order to obtain a good result. Spinal cord stimulation is an invasive but safe and effective treatment for the relief of intractable pain in patients with reflex sympathetic dystrophy.

Also in this issue of the *Journal,* van Hilten and colleagues report on their double-blind, randomized crossover trial comparing intrathecal baclofen, a GABA-receptor agonist (type B), with placebo for the treatment of dystonia in patients with reflex sympathetic dystrophy.[15] In six of seven patients, bolus injections of 50 and 75 μg of baclofen resulted in complete or partial resolution of dystonia of the hands, but little improvement was noted in dystonia of the legs. The patients whose hands were affected regained normal function with prolonged therapy. Pain and violent spasms were also relieved in some patients. The results of this study strongly support the role of GABAergic inhibitory neurons in the pathophysiology of reflex sympathetic dystrophy. The widespread use of baclofen pumps for spasticity has established their safety for long-term treatment.

Reflex sympathetic dystrophy is a devastating, life-altering illness that frequently affects young people. My suggestions for its management are early diagnosis, treatment of any underlying cause, treatment with sympathetic blockade when appropriate, and intensive physical therapy. If these measures fail, the use of dorsal-column stimulation may be helpful, particularly if the disorder is limited to one extremity. My experience also supports the finding of van Hilten et al. that intrathecal baclofen can help relieve dystonia in patients with reflex sympathetic dystrophy, but high doses are usually needed. Although the use of a baclofen pump and dorsal-column stimulation involve invasive procedures, they are welcome additions to the treatment options for patients with severe reflex sympathetic dystrophy.

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