Spinal Cord Stimulation Is Effective in Management of Complex Regional Pain Syndrome I: Fact or Fiction

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BACKGROUND: Complex regional pain syndrome (CRPS) I is a debilitating neuropathic pain disorder characterized by burning pain and allodynia. Spinal cord stimulation (SCS) is effective in the treatment of CRPS I in the medium term but its long-term efficacy and ability to improve functional status remains controversial.

OBJECTIVE: To evaluate the ability of SCS to improve pain, functional status, and quality of life in the long term.

METHODS: We retrospectively analyzed 25 patients over a mean follow-up period of 88 months. The parameters for evaluation were visual analog scale (VAS), Oswestry Disability Index (ODI), Beck Depression Inventory (BDI), EuroQoL-5D (EQ-5D) and Short Form 36 (SF-36), and drug consumption. Evaluations were conducted at point of entry, 3 months, 12 months, and last follow-up at 88 months (mean).

RESULTS: At baseline, the mean scores were VAS 8.4, ODI 70%, BDI 28, EQ-5D 0.30, and SF-36 24. In general, maximum improvement was recorded at follow-up at 3 months (VAS 4.8, ODI 45%, BDI 15, EQ-5D 0.57, and SF-36 45). At last follow-up, scores were 5.6, 50%, 19, 0.57, and 40, respectively. Despite some regression, at last follow-up benefits were maintained and found to be statistically significant ($P < .001$) compared with baseline. Medication usage declined. SCS did not prevent disease spread to other limbs. Best results were achieved in stage I CRPS I, patients under 40 years of age, and those receiving SCS within 1 year of disease onset.

CONCLUSION: SCS improves pain, quality of life, and functional status over the long term and consequently merits early consideration in the treatment continuum.

KEY WORDS: Chronic pain, Complex regional pain syndrome I, Long-term results, Quality of life, Spinal cord stimulation

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Complex regional pain syndrome I (CRPS I) is a debilitating neuropathic pain syndrome of unknown etiology, accompanied by sensory, motor, and autonomic dysfunction and resultant trophic changes over time.[1] According to the International Association for the Study of Pain (IASP), diagnostic criteria are constant burning pain; allodynia or hyperalgesia disproportionate to the inciting noxious event; temperature changes in the affected area; edema; atrophy of hair follicles, nails, and other soft tissues; sudomotor dysfunction; altered skin color; impaired joint mobility; and patchy demineralization of the bone in later stages of pathology.[1] CRPS I is not attributed to a discernable nerve injury.[1] At present, no objective diagnostic tool is available; hence, diagnosis is based mainly on history and clinical evaluation.[2] With the use of the IASP diagnostic criteria, the incidence has been reported to be as high as 26.2 new cases per 100 000 annually.[3] In the majority of cases, patients develop CRPS I after injury or surgery;

ABBREVIATIONS: BDI, Beck Depression Inventory; **CMM,** conventional medical management; **CRPS,** complex regional pain syndrome; **EQ-5D,** EuroQoL-5D; **HrQoL,** health-related quality of life; **IASP,** International Association for the Study of Pain; **MRA,** multiple regression analysis; **ODI,** Oswestry Disability Index; **RCT,** randomized controlled trial; **SCS,** spinal cord stimulation; **SF-36,** Short Form 36; **VAS,** visual analog scale

29% after sprain or strain, 24% following surgery, 23% because of spontaneous or unknown causes, 16% after fractures, and 8% after contusion or crush injuries.[4]

Historically, 3 progressive stages have been described as important in identifying and treating the syndrome. Stage I (acute stage) presents as pain and sensory abnormalities including hyperalgesia and allodynia, signs of vasomotor dysfunction, and prominent edema and sudomotor disturbance.[5] Stage II (dystrophic stage) is characterized by increased pain, sensory dysfunction, and continued evidence of vasomotor dysfunction, with the development of significant motor and trophic changes.[5] Stage III (atrophic stage) is evidenced by decreased pain, continued sensory and vasomotor disturbance, and increased motor and trophic dysfunction.[5] The existence of compartmentalized, sequential staging has not been scientifically proven, but rather is based on clinical experience and case studies. Some patients may not progress to later stages, but others may do so at a variable rate.[1-6]

Although various hypotheses have been put forward, the basic pathophysiology of CRPS I is not clearly understood. There is considerable evidence supporting centralization of the pathophysiology in chronic CRPS I.[7] One such hypothesis, known as the vicious circle concept, proposes that an initial injury to peripheral tissues could lead to a focus of irritability that initiates abnormal firing in the dorsal horn of the spinal cord.[8] The activity in the dorsal horn may then spread via collaterals to the intermediolateral column with a resulting increase in sympathetic activity that is responsible for vasoconstriction, ischemia, and pain, thus inducing a self-sustaining cycle.[8] However, others argue that trauma to peripheral tissue activates unmyelinated C nociceptors and Aδ fibers, which in turn excite wide dynamic range neurons causing them to become more sensitized to subsequent afferent input.[9] It has also been suggested that α-adrenergic receptors mediate pain of sympathetic origin.[10,11] However, sympathetic overactivity is not an absolute requirement in the diagnosis of CRPS I, and the precise role of sympathetic outflow in this phenomenon is not known. In addition, many instances of CRPS I also include myoclonic activity, which is probably the best physical indicator pointing to an underlying central mechanism.[12]

At present, no curative treatment for CRPS I exists. The phenomenon responds poorly to conventional pharmacotherapy and other modalities such as transcutaneous electrical nerve stimulation, chemical blocks, chemical or surgical sympathetectomies, and physical and occupational therapy.[13,14] In contrast, spinal cord stimulation (SCS) therapy has been shown to reduce pain and allodynia and to improve limb function in patients experiencing CRPS I.[15-18]

Initially, the effects of SCS were explained on the basis of gate theory, but the precise mode of action remains unclear.[19] Mechanisms at play during stimulation may include:

1) Suppression of the hyperexcitability of wide dynamic range neurons and high-threshold nociceptive-specific spinothalamic neurons in the dorsal column
2) Activation of interneurons at or in close proximity to the substantia gelatinosa that consequently inhibits the deeper laminae III to V in the dorsal horn
3) Excitation of supraspinal sites such as the pretectal nucleus that, in turn, produces analgesia by inhibiting nociceptive dorsal horn neurons[20-22]

Moreover, SCS is known to produce electrical and chemical alterations as it induces the release of neurotransmitters such as adenosine, glycine, 5-hydroxytryptamine, while also activating γ-aminobutyric $acid_B$ receptors, which, in turn, decrease excitatory amino acids at the level of the dorsal horn cells.[22,23]

The only randomized controlled trial (RCT) published to date, performed by Kemler and colleagues, investigated the effect of SCS in combination with physical therapy (PT) compared with PT alone.[15,24] This study reported that SCS in combination with PT was more effective than PT alone in reducing pain at 6 months and 2 years, but not at 5 years. Similarly, there was also no difference reported in health-related quality of life (HrQoL) between the 2 groups over the entire study period. In attempting to explain their findings, the investigators hypothesized various scenarios: a true pain increase in the SCS group, unknown mechanism of action of SCS, the possibility that patients in the trial period may have exaggerated their pain relief, disease progression to an extent that does not respond as well, and the possibility that the PT group may have shown some spontaneous improvement.[24] The results of this RCT must be weighed against an overwhelming and growing body of evidence of multiple case studies and meta-analyses indicating that SCS improves pain, activity levels, and quality of life in a cost-effective manner.[25-33]

It is clear that the debate around the long-term efficacy of SCS, in terms of its ability to provide pain relief and improve functional outcomes in patients with CRPS I, is far from over. The focus of our earlier publications had been to establish the role of SCS in pain management of CRPS cases.[17,34,35] The limitations of these published studies are small cohort, short follow-up, and minimal emphasis on functional outcomes. In an attempt to provide a long-term perspective and contribute to this debate, we present an analysis of 25 patients with an SCS implanted for the management of CRPS I over a mean follow-up period of 88 months. To the best of our knowledge, this is the longest reported follow-up period in this patient population.

METHODS

Patient Selection

A search of the database (196 patients with SCS) at our institution in Regina, Canada revealed 31 patients who had an SCS implanted for management of CRPS I. Before implantation, these patients had met the IASP-established criteria for CRPS I, with disease duration of at least 6 months, had failed conventional medical management (CMM), and had undergone psychiatric evaluation. Earlier in this series, 3 patients received surgical sympathectomies; however, this practice lost

its appeal because the benefits were transient, lasting only up to 2 years. Of these 31 patients, trial stimulation failed in 3; these 3 patients therefore did not receive permanent SCS implants. Of the 28 remaining patients, 3 patients were lost to follow-up, resulting in a cohort of 25 patients with complete records suitable for the purposes of this report. Patients in whom trial stimulation failed and those who were lost to follow-up were considered as treatment failures for the purpose of survival analysis.

Ethical approval for this study was obtained from the Regina Qu'appelle Health Region Research Ethics Board and University of Saskatchewan Behavioral Research Ethics Board.

Outcome Measures

At our center, data pertaining to the following outcome measures are routinely collected: visual analog scale (VAS), Oswestry Disability Index (ODI), Beck Depression Inventory (BDI), EuroQoL-5D (EQ-5D), Short Form 36 (SF-36), and pain localization drawings. Evaluation of CRPS I is somewhat limited by measures that have not been specifically validated for this population. Medication usage data were obtained from the provincial pharmaceutical database. The database records all medication dispensed by all pharmacies within the province. The only shortcoming is that when the patient travels out of province, these data are not complete. To overcome this issue, we relied on patient self-report for this period. All outcome measures were evaluated by an independent reviewer (pain physician) who was not directly involved in the care of these patients. The VAS was scored on a line from 0 to 10 cm, the higher the score the greater the reported pain intensity. Functional status was determined by use of the ODI. This outcome measure provides a subjective percentage score of the level of functional disability by evaluating 10 routine activities of daily living on a 6-point scale (0-20%, minimal disability; 21-40%, moderate disability; 41-60%, severe disability; 61-80%, crippled; and 81-100%, bedbound).[36] The BDI was used to capture patient mood. Scores range from 0 (no depressive symptoms) to a maximum of 63, indicating severe depression. The BDI is a series of 21 questions to measure the intensity, severity, and depth of depression. It uses a 4-point intensity scale comprising emotional, behavioral, and somatic symptoms.[37] The EQ-5D records self-reported health problems across 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, each of which can take 1 of 3 responses: no problems, some or moderate problems, or extreme problems.[38] An overall utility score is generated based on these domains, with a score ranging from 0 (death) to a maximum of 1.0 (best health scenario).[39] The SF-36 consists of 36 questions, yielding an 8-scale profile of functional health and well-being scores, physical and mental health summary measures, and a composite health utility index.[39,40] EQ-5D and SF-36 were used as measures of HrQoL. These parameters were recorded at implantation (baseline), 3 months and 12 months post-SCS, and at last follow-up (mean, 88 months). At last follow-up patients were also asked, "Are you satisfied with the pain relief provided by your treatment?" and, "Based on your experience so far would you have agreed to this treatment?" Patient pathology was staged according to the criteria set forth by Bonica, which was outlined previously in the introduction.[5]

Surgical Technique

Percutaneous Lead Implantation

Percutaneous spinal electrode implantation was performed under local anesthesia supplemented by conscious sedation. The patient was placed prone with a pillow positioned under the abdomen to open the interspinous space. Dual C-arm fluoroscopic units were positioned.

A 15-gauge Tuohy type needle is introduced and then advanced to the epidural space using a paramedian approach under fluoroscopic control. The "loss of resistance" technique was used to confirm entry into the epidural space and verified by lateral fluoroscopy. A flexible wire guide was inserted through the needle and advanced to the mid-dorsal level to create a passageway for subsequent introduction of the cylindrical electrode. The guidewire is then replaced by the stimulating lead, which could be either a quadripolar or octapolar lead depending on the preference of the implanter.

For lower extremity pain, the electrode is introduced at either L2 to 3 or L3 to 4 and the tip is advanced rostrally to T9 to 11. For upper extremity symptoms, the electrode is introduced at the T4 to 5 level and subsequently advanced to C4 to 7. The final position of the electrode tip is determined by intraoperative stimulation. To obtain the best results, stimulation-induced paresthesia should overlap the territory of the reported pain.

The leads are then externalized for trial stimulation, which is performed using a handheld external programmer. Duration of the trial period is approximately 1 week. Patients who report greater than 50% pain reduction are considered for permanent implantation.

Surgical (Paddle) Lead Implantation

When percutaneous lead implantation is not possible because of anatomical considerations, in cases of recurrent displacement/fracture of previously implanted percutaneous leads, or because of implanter preference, surgical lead placement is considered.

Surgical implantation is performed with the use of either local, spinal,[41,42] or general anesthesia. Spinal anesthesia cannot be used for electrode implants above the midthoracic level for obvious reasons. The patient may be placed either prone or in a lateral decubitus position. A radiograph is taken to identify the desired spinal vertebral bodies. The lead is inserted via a small laminotomy, usually at T9 to 10 or T10 to 11 for lower limb symptoms and at T1 to 2 for upper limb symptoms (the electrode is then advanced to the cervical region with the electrode contact points lying between C4 and C7).

The final positioning of the lead is determined by intraoperative stimulation in cases where the procedure is done under local or spinal analgesia. When the procedure is performed under general anesthesia, the use of somatosensory evoked potentials is necessary.[42] The leads are then externalized for trial stimulation as described previously.

Once it has been decided to proceed with permanent implantation, the patient is returned to the operating room. This procedure is performed with general anesthesia. The distal end of the lead is connected to the pulse generator using new extensions. The pulse generator may be implanted either in the anterior abdominal wall or over the gluteal ("hip pocket") region. The pulse generator is programmed and activated on the following day. Perioperative antibiotic coverage is administered.

The usual stimulation parameters are 60 Hz, pulse width 210 ms, with an amplitude of approximately 2 to 5 volts. The parameters and electrode configuration are individualized for each case. All equipment used in these cases was supplied by Medtronic Inc. (Minneapolis, Minnesota). The pulse generators used were either nonrechargeable, rechargeable, or radiofrequency-based systems.

Data Analysis

We analyzed the impact of age, sex, disease stage, delay from diagnosis to treatment with SCS, and upper limb vs lower limb pain on patient outcomes. As a secondary measure we also evaluated changes in medication use. Analysis was undertaken using SPSS for Windows (version 17, SPSS, Chicago, Illinois). The change in values of the above-mentioned variables from their baseline values to 3 months and 12 months post-SCS, and last follow-up at 88 months were then subjected to statistical evaluation using a paired 2-tailed t test. We used a forward stepwise multiple regression analysis (MRA) formula to identify parameters that statistically predict the effectiveness of SCS in patients with CRPS I. A probability level of $P < 0.05$ was considered significant.

To analyze event history, Kaplan-Meier analysis was performed to estimate basic statistics and a population survival curve from the sample. We performed a Kaplan-Meier analysis to estimate a population survival curve from the sample, as 3 patients did not meet the criteria for permanent spinal cord implant and 3 were lost to follow-up.

RESULTS

Patient Population

The patient population consisted of 12 males and 13 females with a mean age of 51.2 years (range, 32-82 years) over a mean follow-up period of 88 months (range, 18.1-234.6 months; median, 62.96 months). Ten patients presented with upper extremity pain, whereas 15 had lower extremity pain. Before implantation, all patients only had unilateral limb pain; 14 patients presented with stage I pathology, 8 with stage II, and 3 with stage III.

At baseline, before implantation of SCS, our patient population had impaired functional status (mean ODI, 70.18%), were depressed (mean BDI, 27.57), and exhibited poor HrQoL, as evidenced by low EQ-5D utility (mean, 0.30) and SF-36 (mean, 24.20) scores. Similarly, they reported to be in severe pain (mean, VAS 8.42 cm). At 88 months, patients experienced improvements in their level of functional status, as average ODI scores declined to 50.25%. Depression scores dropped from 27.57 to 19.08. HrQoL also improved. EQ-5D rose from 0.31 to an above-average utility score of 0.57 and SF-36 scores increased from 24.16 to 39.61. Pain levels were moderated to 5.58 cm. When comparing VAS, ODI, BDI, EQ-5D, and SF-36 at baseline and last follow-up, the P value was $<.001$. The benefits of SCS slightly regressed over time, but statistically significant improvement persisted over time compared with baseline (Tables 1–7, Figure 1).

Censored and uncensored data are represented by a Kaplan-Meier plot, which displays the cumulative survival function as time passes (Figure 2). Each plateau represents the constant survival probability as time increases. The curve indicates a descending step function with tic marks in the plot used to indicate censorship. In the Kaplan-Meier analysis mean-survival time was 88.03 months, and median survival time remained similar to the arithmetic calculation. This increase in survival times is due to the inclusion of censored data in the analysis.

The Predictive Role of Delayed Treatment and CRPS Staging

MRA revealed moderate-to-strong correlations with increased pain intensity (VAS), depression (BDI), reduced functional status (ODI) and health status (SF-36) when SCS treatment was delayed in excess of 12 months after the diagnosis of CRPS I ($0.6 < |r| < 0.9$). The MRA also confirmed that the greatest improvement in SF-36 and VAS scores occurred in younger patients (those 40 years of age and younger), in stage I CRPS I, who received the intervention within the first year of diagnosis. As anticipated, advancing age was found to have a negative impact on patient health status as measured by the SF-36.

Staging and Functional Status

In our study, although the proportion of males to females was almost equal, females presented with more advanced stage disease. However, sex had no influence on the degree of improvement in VAS, ODI, BDI, EQ-5D, and SF-36 scores over time. The greatest gains in functional status were attained by stage I patients. Before implantation, 3 male patients in the stage I group were gainfully employed. This number had increased to 5 (3 males; 2 females) at last follow-up. None of the patients from other groups were able to enter the workforce.

Patient Satisfaction

Patients were asked, ''Are you satisfied with the pain relief provided by your treatment?'' and, ''Based on your experience so far would you have agreed to this treatment?''; 22 of the 25 patients replied yes to both questions. The 6 patients who did receive an implant or who were lost to follow-up did not participate in this survey.

Complications

Complications related to SCS in this series are presented in Tables 2 and 3. The most common complications were hardware related and consisted of electrode fracturing or displacement, which was corrected by either repositioning or replacement of the electrode. Infection necessitated explanation and reimplantation in the same patient 3 times. This patient was obese, hypertensive, and had poorly controlled diabetes. The pulse generators initially implanted were either nonrechargeable or, in the case of 4 patients, radiofrequency-based systems. Three of these 4 patients were maintained on the radiofrequency-based systems, and the nonrechargeable systems were replaced as needed with nonrechargeable or rechargeable pulse generators. There were no cases of hardware malfunction.

Reduction in Medication Usage

After the initiation of SCS, many patients were able to decrease their drug consumption by at least 25%. This reduction was most

TABLE 1. Patient Demographics[a]

Previously Referenced	Patient ID	Age	Sex	Previous Treatments	Date of First Implant	Follow-up Period (mo)	Date of Last Follow-up
	1	44	F	Peripheral nerve block	19/12/2008	18.1	19/06/2010
	2	53	M	Foot surgery × 6	19/07/2006	22.5	19/05/2008
	3	38	M	Sympathetic nerve block × 3	17/05/2005	38.5	27/06/2009
	4	72	F	Peripheral nerve block	21/02/2005	43.2	21/09/2008
	5	38	M	Sympathetic nerve block	09/01/2005	44.1	09/09/2008
	6	58	F	Sympathetic nerve block	05/11/2004	44.3	05/07/2008
	7	35	F	Sympathetic nerve block	26/08/2004	47.5	26/07/2008
	8	31	F	Sympathetic nerve block	17/05/2004	49.0	17/06/2008
Kumar (2006)[35]	9	36	M	Sympathetic nerve block	10/12/2001	51.0	18/08/2007
Kumar (2006)[35]	10	51	M	Decompression surgery	14/09/2001	51.2	14/12/2005
Kumar (2006)[35]	11	59	F	Back surgery	31/08/2001	53.4	31/01/2006
Kumar (2006)[35]	12	61	M	Sympathetic nerve block	22/09/2000	58.7	22/07/2005
Kumar (2006)[35]	13	42	F	Stellate ganglion blocks	15/09/2000	63.0	15/11/2005
Kumar (2006)[35]	14	49	F	Sympathetic nerve blocks	10/07/2000	77.0	10/12/2006
Kumar (2006)[35]	15	58	F	Sympathetic nerve blocks, laminectomy	09/06/1999	89.0	09/11/2006
Kumar (2006)[35]	16	63	M	Chemical sympathectomy × 2	07/06/1999	93.0	07/03/2007
Kumar (2006)[35]	17	37	F	Shoulder surgery × 15	02/01/1999	95.0	02/12/2006
Kumar (1997),[17] Kumar (1998),[34] Kumar (2006)[35]	18	59	F	Cervical sympathectomy	08/07/1994	98.0	08/09/2002
Kumar (1997),[17] Kumar (1998),[34] Kumar (2006)[35]	19	60	M	Peripheral nerve block, lumbar sympathectomy	23/07/1992	101.0	23/12/2000
Kumar (1997),[17] Kumar (1998),[34] Kumar (2006)[35]	20	45	M	Peripheral nerve block	14/07/1992	103.0	14/02/2001
Kumar (1997),[17] Kumar (1998),[34] Kumar (2006)[35]	21	55	M	Knee surgery × 15	09/09/1991	110.0	09/11/2000
Kumar (1997),[17] Kumar (1998),[34] Kumar (2006)[35]	22	42	M	Peripheral nerve block	31/01/1991	181.0	28/02/2006
Kumar (1997),[17] Kumar (1998),[34] Kumar (2006)[35]	23	42	M	Sympathetic nerve block	08/11/1990	215.0	08/10/2008
Kumar (1997),[17] Kumar (1998),[34] Kumar (2006)[35]	24	82	F	Peripheral nerve block	08/08/1989	217.0	08/09/2007
Kumar (1997),[17] Kumar (1998),[34] Kumar (2006)[35]	25	71	F	Sympathetic nerve blocks, TENS, lumbar sympathectomy	12/07/1989	234.6	12/01/2009

[a]F, female; M, male; TENS, transcutaneous electrical nerve stimulation.

TABLE 2. Employment Status, Medication Usage, Electrode Positioning, and Biological Complication Data[a]

Patient ID	Employment		Drugs Utilized Before SCS	Medication Usage Reduction (>25%)	Time to Implantation (mo)	CRPS I Location	Superior Electrode Contact	Infection	Bleeding
	Prior to SCS	Now							
1	N	Y	OP, NS		2	U	C5	N	N
2	N	N	AC, AD, OP, NS	AD, AC, OP	4	L	T10	N	N
3	Y	Y	AC, AD, OP, NS	AD, AC	4	U	C7	N	N
4	N	N	AC, AD, OP, NS	AD, AC, NS	4.3	L	T10	N	N
5	Y	Y	AC, AD, OP, NS	AD, AC	5	L	T11	N	N
6	N	N	OP, NS	NS	5	L (bilat)	T10	N	N
7	N	Y	AD, AC	AD, AC	6	L	T11	N	N
8	N	N	AC, AD, OP, NS	OP, NS	6	L (bilat)	T10	N	N
9	N	N	AC, AD, OP, NS	AC, AD	6	L	T12	N	N
10	Y	Y	AD, AC	AC	6.2	U	C5	N	N
11	N	N	AD, AC, NS	AD, NS	7	L	T10	N	N
12	N	N	AD, AC, NS	AD, AC	7.1	U	C5	N	N
13	N	N	OP, NS	OP	10	U	C5	N	N
14	N	N	AD, OP	AD	11	U[bc]	C6	N	N
15	N	N	OP, AD, NS	OP, NS	11.7	L	T10	N	N
16	N	N	AD, NS	AD	11.8	L	T10	N	N
17	N	N	AC, AD, OP, NS	AD, AC	11.9	U[d]	C5	N	N
18	N	N	OP		12	U	C2	N	N
19	N	N	OP, NS	NS	12	L	T10	N	N
20	N	N	AD, NS	NS	12.1	U	C4	N	N
21	N	N	AC, AD, OP, NS	AD, AC	13	L[b]	T12	Y(3)	N
22	N	N	AC, AD, OP, NS	AC, NS	15	U	C4	N	N
23	N	N	AC, AD, OP, NS	AD, AC	15	L	T10	N	N
24	N	N	AD, OP, NS	OP, NS	16	L[b]	T10	N	N
25	N	N	AD, OP, NS	OP, NS	23	L	T10	N	N

[a]AC, anticonvulsant; AD, antidepressant; CRPS, complex regional pain syndrome; L, lower extremity; NS, nonsteroidal anti-inflammatory drug; OP, opioid; SCS, spinal cord stimulation; U, upper extremity.
[b]Spread from lower to upper limb.
[c]Mirror spread.
[d]Spread from upper to lower limb.

noticeable in the usage of anticonvulsants, antidepressants, and nonsteroidal anti-inflammatory drugs (Table 2).

Disease Progression

SCS did not appear to prevent the progression of CRPS I. All patients in this series experienced a gradual enlargement in the affected area over time (contiguous spread).[43] In 3 cases there was spread of the disease from lower to upper limb and in 1 case, of upper to lower limb (independent spread).[43] Independent spread occurred within 1 year of implantation. In 1 patient there was spread of pathology to the contralateral lower limb (mirror spread).[43]

Patient Outcomes in Upper vs Lower Limb CRPS I

In the evaluation of the outcome measures, no statistically significant differences were identified, indicating that SCS therapy was equally efficacious in patients with upper or lower limb pathology.

DISCUSSION

SCS is a safe, reversible, cost-effective, and minimally invasive intervention that is capable of generating superior outcomes for the treatment of neuropathic pain.[17,18,25-33] Increasingly, a large body of evidence is accumulating that supports the application of SCS in a diverse array of clinical scenarios. The benefits of SCS are well established in the treatment for pain that results from failed back surgery syndrome, peripheral neuropathy, peripheral vascular disease, and phantom limb pain.[44-49] The beneficial effects of SCS on pain scores, activity levels and function, and depressive symptoms are well known.[17,18,34,50-54] In CRPS I, SCS reduces pain but the degree of improvement in quality of life remains controversial.[15-18,24,31,32,54-56]

Despite these encouraging findings, the enthusiasm for SCS in the management of CRPS I has been tempered by the small cohorts and short follow-up periods of studies conducted to date.[28,16,50,54,55] This study is an attempt to fill this void. To

TABLE 3. Hardware Complications

Patient ID	Type of 1st Electrode	Repositioning	Electrode Fracture	Electrode Repositioning	Electrode Replacement	Electrode Type (Replaced By)	Type of 1st Battery	Date of 1st Battery Depletion
1	Octapolar	N					Restore	
2	Pisces–Quad	N					Itrel–III	
3	Pisces–Quad	N			27/04/2006	Specify	Itrel–III	
4	Pisces–Quad	N					Itrel–III	19/01/2007
5	Pisces–Quad	N					Itrel–III	
6	Pisces–Quad	N					Itrel–III	30/03/2007
7	Pisces–Quad	N					Itrel–III	01/11/2006
8	Pisces–Quad	Y(1)		19/05/2005	19/05/2005	Resume	Itrel–III	
9	Pisces–Quad	N			18/05/2003	Specify	Itrel–III	
10	Pisces–Quad	Y(2)		13/02/2003; 25/02/2004			Itrel–III	03/11/2006
11	Pisces–Quad	N					Itrel–III	17/05/2004
12	Pisces–Quad	N					Itrel–III	
13	Pisces–Quad	Y(1)		31/05/2002			Itrel–III	31/05/2004
14	Pisces–Quad	N					Itrel–II	01/03/2006
15	Pisces–Quad	N					Itrel–II	31/08/2004
16	Pisces–Quad	N					Itrel–II	23/11/2001
17	Resume II	N		01/05/2001	23/05/2002	Pisces–Quad	Itrel–II	
18	Pisces–Quad	N					Xtrel	
19	Pisces–Quad	N					Xtrel	
20	Pisces–Quad	N			09/06/1997		Itrel–II	
21	Resume	Y(1)			13/05/2004	Resume	Xtrel	09/03/1992
					16/09/2004	Resume		
					10/09/2010	5-6-5 lead		
22	Pisces–Quad	N			31/01/1991			
23	Pisces–Quad	N					Itrel–II	
24	Pisces–Quad	Y(1)		01/09/1992	27/06/1996			
25	Sigma–Pisces	N	14/08/1995		27/09/1995	Pisces–Quad	Xtrel	

the best of our knowledge, this study has the longest follow-up period in the literature. The only RCT on the subject revealed that SCS in combination with PT was more effective than PT alone in reducing pain at 6 months and 2 years but that no difference was detected at the fifth year of follow-up.[24] Kemler and colleagues go on to state that the effectiveness of SCS lasts between 2 and 3 years. Our study confirms that the benefits of SCS are maintained, despite some regression, over the lengthy follow-up period of 88 months (mean). It is difficult to compare Kemler and colleagues' results with our own in every aspect. The differences reported may be attributable to factors such as age, staging, and the severity of pathology at the time of implantation. Whereas the mean age of patients included in the Kemler et al study is younger, it is not clear as to the duration or the severity of disease faced by their patients. Looking to the population base and documented functional impairment, it appears that these patients were possibly in an advanced stage of CRPS I. Age, when taken into consideration with severity and stage of disease, does have an impact on patient outcomes, potentially explaining the discrepancy between their results and ours. The relationship between age and disease severity is demonstrated by our regression analysis. Similar to Kemler et al, all patients included in our study had previously tried and subsequently failed CMM.

Throughout the follow-up period we found that SCS was a well-tolerated intervention that provides pain relief, enhances functional status, and improves HrQoL. This study demonstrates that, typically, maximum benefit was evident by the first year of implantation with slight decline in the parameters over time. Despite this, the improvements at last follow-up were statistically significant compared with baseline. Although the improvements in outcome measures may appear suboptimal at face value, they are considered clinically relevant, as attested by high patient satisfaction. Regression over time is not uncommon with SCS and is likely a reflection of the chronicity of disease and the fact that SCS is not curative.[34,44,46,47,55,57]

A direct comparison with other studies is challenging because of the short follow-up periods of most studies. Harke et al,[27] in their prospective trial, found no regression at 3, 6, 9, or 12 months post-SCS on pain intensity. In a study of 10 consecutive

TABLE 4. Pulse Generator Replacements

Patient ID	Date of Implant of 2nd Battery	Type of 2nd Battery	Date of Implant of 3rd Battery	Type of 3rd Battery	Date of Implant of 4th Battery	Type of 4th Battery
1						
2						
3		Synergy				
4	25/01/2007	Itrel–III	02/07/2008	Synergy		
5						
6	09/05/2007	Itrel–II				
7	08/03/2007	Restore				
8						
9	27/08/2008	Synergy				
10	21/11/2006					
11	22/06/2004	Itrel–III	08/07/2008	Itrel–III		
12						
13	22/06/2004	Itrel–III				
14	08/03/2006	Itrel–III				
15	14/09/2004	Itrel–III	02/02/2007	Restore		
16	30/01/2002	Itrel–III				
17						
18						
19						
20						
21	09/03/1992	Itrel–II	27/01/2006	Itrel–III	01/10/2009	Restore
22						
23						
24						
25						

cases of CRPS I, Verdolin et al[16] identified stable improvements in pain scores 3 and 6 months post-SCS. However, Forouzanfar et al[55] reported a decline in pain relief after 2 years of follow-up. For additional context, we reviewed 3 meta-analyses. Taylor et al[33] summarized that, on average, 67% of patients with implants achieved a pain relief of at least 50%, and the mean pooled reduction of VAS score was 4.7. Grabow et al[26] reported a baseline VAS score range of 6.7 to 8.3, which at the end of the follow-up period (6-45.6 months) was 1.3 to 4.5. Turner combined CRPS I results with those of failed back surgery syndrome, making it difficult to scrutinize the benefits of SCS in CRPS I alone, but the reported results are similarly encouraging.[58] In addition, in our study, SCS was found to be equally efficacious in upper limb vs lower limb CRPS I, in keeping with findings of Forouzanfar and colleagues.[55]

In this study, almost equal numbers of males and females enrolled; however, this may be a coincidental finding, even though literature indicates that CRPS I is more commonly seen in women, in ratios of 2.3 to 4.5:1.[4,59,60] What leads to the increased incidence of CRPS I in females and whether there is an associated hormonal interplay is not known. In this series females presented with more advanced stage disease. However, the degree of improvement in the various scores throughout the course of this study was not affects by sex.

The argument in favor of SCS therapy is further buoyed by high patient satisfaction and low complication rates. Twenty-two of the 25 patients surveyed were satisfied with the treatment, indicating a willingness to repeat the procedure if necessary based on their present experience. Our high satisfaction rates are in line with published reports.[24,35,44,52,53,56,61,62] This reinforces the usefulness of SCS in the management of CRPS I.

In this series, the majority of complications were hardware related, such as electrode fracturing or displacement, and were easily correctable by lead replacement or repositioning, respectively. Infection was treated with appropriate antibiotic therapy, but one case required removal of hardware and subsequent reimplantation. This occurred in 1 patient because of underlying comorbid conditions. Of note is the cost-effectiveness of SCS, which is established in the case of CRPS I.[29,33]

Patients affected by CRPS I consume large doses of analgesics, narcotics, and/or anticonvulsants to manage pain. In our series, after the initiation of SCS therapy there was a reduction in medication usage compared with pre-SCS levels (Table 2). The ability of SCS to reduce drug usage has not been well-studied, but the preliminary results from previous research paint a positive picture.[16,18,27]

All patients experienced some degree of contiguous spread over time. In addition, spread from one limb to another was

TABLE 5. Patient Outcome Measures: VAS, ODI, and BDI[a]

	VAS				ODI				BDI			
Patient ID	Baseline	3 Months	12 Months	88 Months	Baseline	3 Months	12 Months	88 Months	Baseline	3 Months	12 Months	88 Months
1	5.1	1.8	0.4	3.9	38.5	5.2	3.3	18.0	3.1	0.3	1.3	0.1
2	6.0	1.8	1.3	2.2	51.8	11.4	20.0	24.7	4.5	1.1	1.3	0.6
3	6.6	2.0	3.4	2.6	54.2	14.3	21.7	33.7	4.6	1.3	4.8	1.0
4	6.9	2.1	3.5	2.8	55.0	14.6	30.4	34.1	5.8	3.8	5.6	2.2
5	7.1	2.5	3.9	4.3	55.7	16.2	35.9	36.7	7.2	4.5	8.2	2.5
6	7.3	2.8	3.9	3.3	62.3	26.4	39.0	38.2	8.5	4.9	9.4	3.9
7	7.6	3.1	4.3	3.3	65.4	30.1	40.5	40.3	13.3	6.1	9.5	5.4
8	7.8	5.4	4.3	4.4	67.2	32.3	40.7	40.4	20.1	6.9	11.7	8.2
9	8.2	4.9	4.4	4.5	67.5	41.2	42.9	41.6	22.6	7.3	12.0	11.9
10	8.3	3.9	4.6	5.6	69.4	44.2	44.0	43.1	23.2	8.5	14.6	14.5
11	8.5	4.2	4.8	5.6	69.5	44.7	44.2	45.4	27.1	9.0	14.6	15.6
12	8.6	4.5	4.9	5.9	69.6	46.2	44.7	47.2	27.9	9.7	15.4	18.1
13	8.7	4.7	5.2	5.9	69.7	48.2	44.7	49.1	28.2	11.0	15.6	18.9
14	8.8	5.0	5.5	6.0	71.7	50.4	45.3	49.3	29.8	11.6	17.2	19.1
15	9.0	5.4	5.8	6.0	72.6	52.9	47.3	50.5	30.9	12.0	18.5	20.5
16	9.1	5.5	5.9	6.2	73.1	53.2	48.7	52.6	31.5	13.0	20.3	22.2
17	9.2	5.8	6.0	6.3	75.4	55.1	53.0	59.2	31.8	13.5	21.2	25.8
18	9.3	6.2	6.3	6.6	78.3	56.0	56.8	61.6	33.9	16.6	21.7	27.9
19	9.3	6.3	6.4	6.9	78.4	58.5	60.2	63.3	35.1	19.1	22.0	28.6
20	9.3	6.6	6.6	6.9	79.5	59.4	61.2	63.5	36.6	19.8	22.8	29.0
21	9.6	7.2	7.0	7.5	80.1	60.0	62.0	65.2	40.9	22.4	23.5	29.6
22	9.8	7.2	7.3	7.9	83.9	64.4	65.3	72.7	42.5	23.0	24.2	29.8
23	10.0	7.3	7.5	8.5	85.8	70.9	69.2	72.9	55.0	39.4	26.9	38.6
24	10.0	7.0	7.4	8.3	87.9	76.2	72.9	76.0	62.1	43.6	37.8	47.8
25	10.0	7.1	7.6	8.3	92.1	83.5	86.5	76.9	63.0	60.0	38.3	55.1

[a]BDI, Beck Depression Inventory; ODI, Oswestry Disability Index; VAS, visual analog scale.

found in 4 of 25 patients (4 cases of independent spread; 1 case of mirror spread). Independent spread occurred within 1 year of implantation. Maleki and colleagues[43] examined the pattern of disease spread and found that all patients experienced contiguous spread, whereas 70% also had independent spread, 11% also had mirror spread, and 1 patient had all 3 kinds of spread.[43] It is postulated that CRPS I spread may be multifactorial, implicating factors such as generalized susceptibility, abnormal spread via commissural pathways, or aberrant central nervous system regulation of neurogenic inflammation.[43] There is a paucity of literature related to the timing and pattern of spread. Recently, the existence of a "neural switch" has been postulated. In 1 case series, complete symptom resolution was observed 1 month after implantation and stimulation was discontinued without recurrence over the 1-year follow-up period.[63] In another investigation, SCS resulted in pain alleviation in 5 of 7 adolescent girls aged 11 to 14.[64]

Timing of Treatment

MRA indicates that longer delays in seeking treatment or treatment at a later stage of the disease hinders optimal pain relief, and limits improvements in functional status and depression. Pain relief and health status improvement was best achieved in those with stage I pathology, those 40 years of age or younger, and those receiving treatment within the first year of symptom onset, highlighting the benefits of early implantation.

In this study, 2 patients, who were previously unemployed, returned to the workforce. Three patients who were working continued to do so. Harke et al,[27] in their prospective trial, recorded an impressive 70% back-to-work rate; such an impressive result has not been duplicated by other investigators and could be a reflection of the enrollment of patients in the early phase of the disease.

There is an emerging stream of thought that favors more aggressive use of neurostimulation at an earlier stage before permanent dystrophic changes develop.[65] The IASP Expert Group recommends that SCS be instituted within 12 to 16 weeks if conventional treatment fails.[31,32]

Study Limitations

This study is limited by the lack of a control group, blinding, and a limited patient population. Typically, the absence of a placebo group leads to an overestimation of treatment efficacy. RCTs are difficult to conduct in this population, which is evident

TABLE 6. Patient Outcome Measures: EQ-5D and SF-36[a]

	EQ-5D				SF-36 (Aggregate Scores)			
Patient ID	Baseline	3 Months	12 Months	88 Months	Baseline	3 Months	12 Months	88 Months
1	0.6	0.9	1.1	1.1	53.9	90.8	82.6	72.0
2	0.5	0.9	0.9	0.9	47.3	94.6	65.0	60.6
3	0.5	0.9	0.9	0.9	44.1	82.8	60.7	58.3
4	0.5	0.9	0.8	0.8	43.0	73.0	56.8	54.2
5	0.4	0.8	0.8	0.8	32.5	69.8	53.8	57.1
6	0.4	0.8	0.8	0.8	31.3	64.6	53.4	52.6
7	0.4	0.8	0.8	0.7	31.3	56.2	51.0	50.4
8	0.4	0.8	0.7	0.7	30.7	55.5	50.8	49.7
9	0.3	0.8	0.7	0.6	29.6	47.5	50.8	47.8
10	0.3	0.7	0.7	0.6	26.1	47.5	50.3	47.1
11	0.3	0.7	0.6	0.6	23.1	41.8	49.9	43.2
12	0.3	0.7	0.6	0.6	22.2	40.2	49.3	40.5
13	0.3	0.7	0.6	0.6	22.0	38.5	47.8	39.4
14	0.3	0.7	0.5	0.5	21.9	37.2	45.9	35.9
15	0.3	0.6	0.5	0.5	20.4	36.8	38.3	34.1
16	0.3	0.6	0.5	0.5	17.7	34.9	37.9	31.4
17	0.3	0.6	0.5	0.5	16.7	34.7	32.5	30.5
18	0.2	0.6	0.5	0.5	16.0	26.5	25.3	30.2
19	0.2	0.5	0.4	0.5	14.0	26.4	24.0	29.3
20	0.2	0.5	0.4	0.4	12.2	25.7	23.0	26.4
21	0.2	0.5	0.4	0.3	11.2	20.3	22.8	25.0
22	0.1	0.5	0.4	0.3	10.5	20.0	22.3	24.2
23	0.1	0.5	0.4	0.2	10.3	19.2	21.1	21.7
24	0.1	0.3	0.3	0.2	9.4	16.6	20.2	14.0
25	0.1	0.3	0.3	0.1	6.5	14.4	10.0	15.0

[a]EQ-5D, EuroQoL-5D; SF-36, Short Form 36.

by the existence of only one RCT published to date. In our situation, patients had already undergone extensive CMM previously, which had proved ineffective, making an RCT with a CMM (including PT) control virtually impossible. In general, this patient population is reluctant to be randomly assigned to studies because of the unbearable pain that they have been experiencing for so long despite CMM. In addition, blinding is difficult, because SCS produces a paresthesia that is perceived by the patient. Although this study does not definitively answer all the questions, the strength of this case series lies in the fact that it

TABLE 7. Patient Outcome Data (Aggregate)[a]

	VAS				ODI				BDI			
	Baseline	3 Months	12 Months	88 Months	Baseline	3 Months	12 Months	88 Months	Baseline	3 Months	12 Months	88 Months
Mean	8.4[b]	4.8[b]	5.1[b]	5.6[b]	70.2[b]	44.6[b]	47.2[b]	50.3[b]	27.6[b]	14.7[b]	16.7[b]	19.1[b]
Std. Error	0.3	0.4	0.4	0.4	2.5	4.2	3.6	3.2	3.4	2.9	1.9	3.0

	EQ-5D				SF-36			
	Baseline	3 Months	12 Months	88 Months	Baseline	3 Months	12 Months	88 Months
Mean	0.30[b]	0.67[b]	0.60[b]	0.57[b]	24.2[b]	44.6[b]	41.8[b]	39.6[b]
Std. Error	0.03	0.04	0.04	0.05	2.6	4.7	3.5	3.0

[a]BDI, Beck Depression Inventory; EQ-5D, EuroQoL-5D; ODI, Oswestry Disability Index; SF-36, Short Form 36; VAS, visual analog scale.
[b]Statistically significant $P < .001$ (2-tailed).

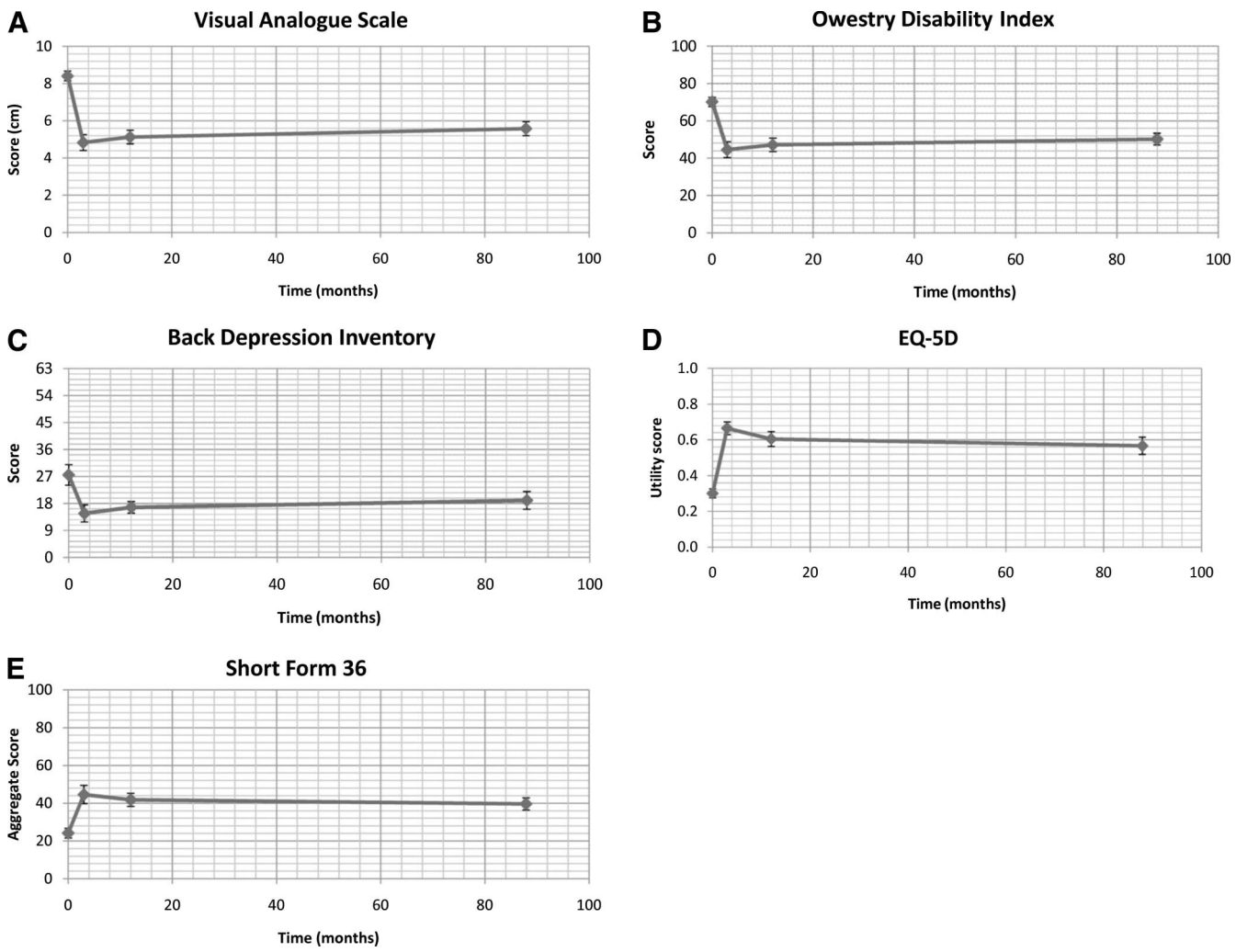

FIGURE 1. **A**, *graph depicting pain relief over the study period, as measured by the visual analog scale (error bars indicate standard error).* P *value (baseline vs last follow-up)* $< .001$. **B**, *graph depicting functional status over the study period, as measured by the Oswestry Disability Index (error bars indicate standard error).* P *value (baseline vs last follow-up)* $< .001$. **C**, *graph depicting levels of depression over the study period, as measured by the Beck Depression Inventory (error bars indicate standard error).* P *value (baseline vs last follow-up)* $< .001$. **D**, *graph depicting health-related quality of life over the study period, as measured by the EuroQol-5 Dimensions (EQ-5D) (error bars indicate standard error).* P *value (baseline vs last follow-up)* $< .001$. **E**, *graph depicting health-related quality of life over the study period, as measured by Short Form-36 (error bars indicate standard error). P value (baseline vs last follow-up)* $< .001$.

is the longest follow-up reported thus far; it has a medium-sized cohort, with few patients lost to follow-up; and the validation of results by an independent investigator. It is acknowledged that further research is required.

CONCLUSION

SCS delivers durable pain relief, enhances functional status, and improves HrQoL. MRA indicates that treatment delay exceeding 1 year limits its effectiveness. The greatest improvement in health status and pain relief occurred in patients with stage I pathology, who were 40 years of age or younger, and in whom the intervention was conducted within 1 year of the onset of symptomatology. SCS does not appear to prevent disease spread to the ipsi- or contralateral limb. On this basis, it is recommended that SCS be considered earlier in the treatment continuum in order to maximize patient outcomes and the opportunity for successful rehabilitation.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

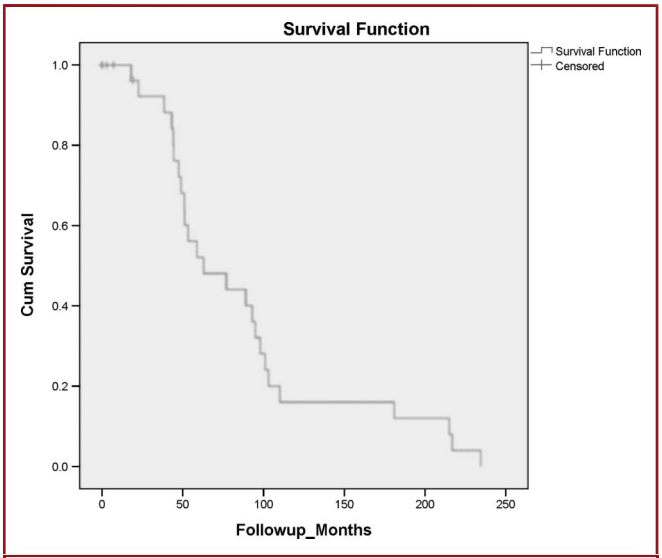

FIGURE 2. *Kaplan-Meier estimates of survival function. Mean, 88.03 months; median, 62.96 months. Cum survival, cumulative survival function.*

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COMMENTS

This article describes the results of spinal cord stimulation (SCS) in 25 patients with complex regional pain syndrome (CRPS-1). Three additional cases failed a percutaneous trial period and 3 more were not available for follow-up. Some of the 25 cases commenced treatment as long as 20 years ago (1990 - 1991) and were last evaluated approximately 10 years ago (last follow-up, 2000). Seventeen of the 25 cases were published once previously, and 8 were published 3 times before now. Two of the 3 previous articles appeared in this journal. Readers may wish notice a few other points as well.

The diagnosis of CRPS-1 – and even its existence as a genuine disorder – engenders skepticism despite the existence of an ICD-9 code. Splitting CRPS-I (reflex sympathetic dystrophy, RSD) from CRPS-II (causalgia) has provided diagnostic legitimacy for a cohort of patients in industrialized Western countries who are predominantly middle-aged Caucasians (in some series, mostly women) who complain of regional pain that affects one or more body parts in the setting of a trivial soft tissue injury (or no injury), and without a neuroanatomical basis or pattern. Moreover, in defiance of conventional neuroanatomy and physiology, CRPS can spread from one body part to another. It is nearly impossible for a clinician to rule out CRPS-1 as a diagnosis for otherwise inexplicable pain complaints. These are not the patients that Mitchell, Morehouse & Keen had in mind nearly 150 years ago. [1] Although trivial soft-tissue injuries have troubled our ancestors since pre-historic times, the recent emergence of CRPS-I as a distinct nosologic entity has coincided with the growth of interventional pain medicine. Genuinely organic cases of persistent pain after paper cuts, hang-nails, or similarly trivial injuries may exist, but the demographics of CRPS-I and the permissive way the diagnosis is applied arguably suggest a predominantly socio-cognitive and behavioral disorder. A skeptical reviewer of CRPS diagnoses in case series and clinical trials might raise the question of what it is – besides inexplicable and/or questionably physiological complaints – that physicians are treating?

Physician-patient relationships are influenced by governmental and/or insurance regulations and social policies. Most pain patients depend upon a physician's authority to approve or supply tangible benefits that include disability payments and insurance coverage, absence- or modification of work duties, opioid and other drug prescriptions, and referrals for physical therapy or other sensorial and pleasant ancillary treatments. An important intangible benefit for patients is validation of their illness status. This cycle of expectations and rewards is a feature of human behavior that provides incentives for caregivers and patients to reinforce each others' beliefs. Such ordinary behavioral and cognitive phenomena are among the reasons why the most informative clinical research projects employ control groups and blinding. Ordinary socio-cognitive influences should not be confused with placebo effects, which only can be observed in blinded trials that employ a sham-treatment group.

Another feature of the neurostimulation pain literature is that it does not really say what most authors and reviewers say it says. In the present

article, the mean change in VAS between 8.4 cm at baseline and 5.6 cm at 88 months (2.8 cm difference) amounts to a 33 percent aggregate reduction in pain intensity. Even at 3 months - the high point in efficacy before a decay set in over time - the difference in VAS compared to baseline was 3.6 cm (8.4 minus 4.8) - equivalent to a 42.8 percent reduction in pain intensity. An historically accepted success criterion in stimulation studies for pain is that at least 50 percent of individual patients should report at least 50 percent pain relief on a numerical or visual scale at follow-up. [2] Until recently, minor variations of the 50:50 standard were used in most trials and studies. As with the Kemler et al trial. [3-5] and other case series or trials of SCS (or other neurostimulation therapies) for pain over the past 40 years, none – including the present article - has reported 50 percent long-term relief in 50 percent of subjects unless efficacy was analyzed without regard for sound biostatistical principles. Then there's the matter of denominators. The figures, legends and text do not clearly inform readers whether or not 6 patients – the 3 who failed test stimulation and 3 more who did not keep follow-up appointments – are counted as treatment failures (e.g., last observation carried forward or some other robust calculation method).

Multiple statistical endpoints and secondary measures sometimes can distract readers from the essential matter of clinically meaningful analgesic efficacy. To-date, post-hoc explorations of statistical differences among multiple non-analgesic endpoints have failed to identify reliable prognostic factors for long-term pain relief. As in most other reports, patient satisfaction and quality of life measures revealed disproportionately high scores compared to modest analgesic efficacy. Rather than supporting the analgesic efficacy of SCS for CRPS-1, another plausible interpretation may be that patients were satisfied because they received a variety of insurance-, compensation-, or lifestyle-related benefits in addition to validation of their illness status. The beneficial effects of a relationship with optimistic caregivers also should not be underestimated.

Finally, it may be worth thinking about whether adequately randomized controlled and blinded clinical trials of SCS and other neurostimulation therapies are possible (the answer is yes) or worthwhile (the answer is probably not). Twenty years ago Marchand et al studied the efficacy of SCS in a randomized, blinded, controlled laboratory and clinical investigation of 8 patients who reported an average pain relief of 63 percent after at least 2 years on therapy. [6] Each patient's customary stimulator settings were used in the laboratory and clinical phases as the treatment arm. Sham stimulation with the amplitude "off" - plus clever and elaborate deception - was the control. "All patients reported a sensation, when in fact no stimulation was given" during the control phase. Laboratory assessments employed standard thermal stimuli. The average difference between active SCS and sham stimulation in the laboratory experiment was 20-28 percent. Blinded outpatient clinical assessments over several days revealed an effect size of active versus sham SCS of 23 - 30 percent on various pain dimensions. Thus, adequate randomization and blinding of neurostimulation pain therapies for clinical trial purposes is possible and already has been implemented successfully, albeit on a small scale for SCS, DBS and TENS. [6-9] The results all pointed in the same direction - namely, that patient-reported analgesic effects were very small, regardless of whether the device was on or off. The fact that no clinical trial or case series to-date has yielded an adequate and clinically meaningful responder rate (according to the historical 50:50 standard) seriously calls into question whether it is worthwhile for industry or academic bodies to sponsor additional level-1 randomized, blinded, and controlled studies. Recent well-designed, randomized, controlled, and effectively blinded (unpublished) industry-sponsored trials of SCS for angina pectoris, occipital nerve stimulation for headache disorders, and motor cortex stimulation for central post-stroke- or trigeminal neuropathic pain also have not revealed convincing analgesic efficacy. Thus, an admittedly counter-intuitive and minority assessment might find that randomized, controlled, and adequately blinded trials of SCS and other stimulation modalities for pain are at risk of failure to show sufficient efficacy to warrant regulatory approval or insurance reimbursement in the US market. The authors may have overreached by concluding that additional patients should be treated, and earlier in their clinical course.

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This retrospective study confirms the efficiency of spinal cord stimulation in the treatment of CRPS I. Moreover, it demonstrates that pain relief and quality of life improvement can be maintained significantly for a long period even though it declines slightly. The authors report the longest follow-up period in this pathology. Thus, it is the first study to include the natural history of the disease in the evaluation, to discuss the impact of spinal cord stimulation on it and to determine prognostic factors.

Nevertheless, these results need to be confirmed by prospective studies to elude the bias engendered by retrospective designs. For example, the population described is not typical, 13 males for 12 females, whereas this pathology is more commonly seen in women (1/4-5). We can assume that the selection of the population could have been biased in some way. The range of follow-up duration is very wide, from 18 to 234 months. A more homogeneous follow-up could help support the conclusions. As it was pointed out by the authors, randomization is difficult to conduct, though possible, because of the reluctance of this population to be included in the placebo group and the fact that SCS has to induce paresthesia to be efficient which limits the placebo effect. A comparative prospective study could be an intermediate solution.

A significant pain improvement has been observed (mean VAS decreasing from 8.42 cm to 5.58 cm). While all the patients implanted seemed satisfied, a VAS between 5 cm and 6 cm reveals a medium to high level of pain. For the Oswestry index, the mean ODI declined from 70.18% to 50.25%. Still an ODI of 50% or more is considered as major

disability. This might be due to the fact that almost half of the patients included experienced a stage II or III. Meanwhile, the best results have been observed for the patients in stage I. The global management of patients suffering from CRPS I may then be reconsidered. SCS might become a complementary tool in the management of early phases whereas its benefit is nowadays underestimated and limited to a last-chance therapy subsequent to medical treatment failure. During the follow-up period, all patients have experienced some degree of disease spread over time. Although no difference has been shown between patients in stage I or II/III, it would be interesting to sort out with a larger cohort whether early implantation can limit this disease spread or not, and modify the natural history of the pathology.

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Carl Friedrich Gauss.

Sometimes referred to as the Princeps mathematicorum, Gauss had a remarkable influence in many fields of mathematics and science and is ranked as one of history's most influential mathematicians. Gaussian functions are widely used in statistics where they describe the normal distributions, in signal processing where they serve to define Gaussian filters, in image processing where two-dimensional Gaussians are used for Gaussian blurs, and in mathematics where they are used to solve heat equations and diffusion equations and to define the Weierstrass transform.