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# Long-term results of peripheral nerve stimulation for reflex sympathetic dystrophy

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✓ This prospective, consecutive series describes peripheral nerve stimulation (PNS) for treatment of severe reflex sympathetic dystrophy (RSD) or complex regional pain syndrome, in patients with symptoms entirely or mainly in the distribution of one major peripheral nerve. Plate-type electrodes were placed surgically on affected nerves and tested for 2 to 4 days. Programmable generators were implanted if 50% or more pain reduction and objective improvement in physical changes were achieved. Patients were followed for 2 to 4 years and a disinterested third-party interviewer performed final patient evaluations. Of 32 patients tested, 30 (94%) underwent permanent PNS placement. Long-term good or fair relief was experienced in 19 (63%) of 30 patients. In successfully treated patients, allodynic and spontaneous pain was reduced on a scale of 10 from 8.3 ± 0.3 preimplantation to 3.5 ± 0.4 (mean ± standard error of the mean) at latest follow up ($p < 0.001$). Changes in vasomotor tone and patient activity levels were markedly improved but motor weakness and trophic changes showed less improvement. Six (20%) of the 30 patients undergoing PNS placement returned to part-time or full-time work after being unemployed prestimulator implantation. Initial involvement of more than one major peripheral nerve correlated with a poor or no relief rating ($p < 0.01$). Operative modifications that minimize technical complications are described. This study indicates that PNS can provide good relief for RSD that is limited to the distribution of one major nerve.

KEY WORDS • peripheral nerve stimulator • reflex sympathetic dystrophy • complex regional pain syndrome

MANY patients diagnosed with reflex sympathetic dystrophy (RSD)[2,11] or complex regional pain syndrome (CRPS) according to the most recent taxonomy[21,34] can be treated successfully with medications, blocks, or infusions.[3,14,29,32] In approximately 50% to 70% of patients with severe RSD, electrical stimulation of the spinal cord is reported to be effective in treating pain, vasomotor changes, and trophic changes.[1,4,31]

Peripheral nerve stimulation (PNS) is another modality that has been described in the treatment of severe RSD.[16,17,25–27] However, there is a paucity of published reports describing the long-term success rates, criteria for success, and technical complications for this modality. This report presents a prospective, consecutive series of patients who have severe RSD with symptoms entirely or mainly in the distribution of one major peripheral nerve and have been treated with PNS. Good long-term symptom relief was observed, and the experience provides important information about patient application and operative techniques.

## Clinical Material and Methods

### *Study Design*

This study was designed to be a Phase I/II evaluation to test the efficacy of PNS in patients who have failed and/or are not eligible for other RSD treatments except spinal cord stimulation (SCS). A PNS trial was offered if the patient's symptoms were entirely or mainly in the distribution of one major peripheral nerve. Each patient underwent a 2-day screening period with the electrode in place, with evaluation of any improvement in pain and/or physical examination changes. The hypothesis of the study was that PNS would be: 1) very effective in reducing or eliminating both mechanical allodynia and spontaneous deep pain; 2) moderately effective in improving vasomotor tone changes; 3) mildly effective in improving motor deficits; and 4) most effective in patients with symptoms and findings entirely in the distribution of one major peripheral nerve.

*Patient Eligibility*

All patients in this study had a diagnosis of RSD based on the following symptoms: 1) light touch–induced allodynia that spreads beyond the area of stimulation and persists after the stimulus; 2) deep burning pain; 3) clinical evidence of vasomotor tone changes; 4) at least some evidence of trophic changes and motor weakness; 5) systematic temperature side differences by thermography with cold pressor responses; and 6) temporary improvement after sympathetic blocks. Vasomotor changes were assessed by thermographic changes, skin color changes, and swelling in comparison to other limbs. Almost all patients had a history of some trauma to the affected nerve, although this was not required for eligibility. Using these criteria, all patients were classified as Stage III RSD.[2]

The patients presented between October 1990 and November 1992, and were screened thoroughly using a multidisciplinary evaluation. They were treated initially with nonnarcotic medications, including adrenergic blocking compounds, antiarrhythmic, antidepressant agents, calcium-channel blocking, and antiinflammatory drugs. All patients received aggressive occupational and physical therapy and various blocks. Patients who failed to obtain adequate pain relief from these treatments were considered for PNS if their pain was entirely or mainly in the distribution of one major peripheral nerve.

*Stage I: Patient Screening*

In Stage I operations, an electrode (Resume; Medtronic, Inc., Minneapolis, MN) with a layer of free fascia covering its surface was placed in apposition to the target nerve. Target nerves were exposed surgically in the following areas: 1) median/ulnar just proximal to the midhumerus in the brachial groove; 2) radial at the midhumerus in the spiral groove; 3) common peroneal superior to the popliteal space under the biceps femoris muscle and tendon; and 4) posterior tibial proximal to the medial malleolus of the ankle. During a 2-day screening period, stimulation parameters were adjusted and records made of pain severity, activity levels, and narcotic usage. Using a verbal digital scale, pain was assessed by asking the question: "On a scale of zero to 10, where zero equals no pain and 10 represents the worst pain that you could imagine, what is your pain now?"

*Stage II: Placement of Generator*

If at least 50% reduction in pain and objective improvement in the physical examination changes were achieved, a permanent implanted generator (Itrel II; Medtronic Inc.) was connected to the electrode. The implanted generator was programmed initially to a pulse rate of 75 Hz, a width of 210 msec, and an electrode combination with the No. 0 electrode negative and the No. 3 electrode positive.

*Follow-Up Evaluation*

After discharge from the hospital, patients were seen every 2 to 6 weeks. A good result was defined as pain reduction of 50% or more, and improvements in at least two of the three physical change categories (vasomotor tone, trophic changes, somatic motor changes). A fair result was defined as pain reduction of 50% or more and improvement in none or one of the three physical change categories, or pain reduction of 25% to 49% and improvement in at least one of the three physical change categories. A poor result was concluded if pain reduction was 25% to 49% without improvement in any of the categories, or pain reduction was less than 25% and improvement was seen in at least one of the categories. All other patients were considered to have had no pain relief at long-term follow up. Using the method of North, *et al.*,[23] the most recent evaluation of the successfully treated patients was conducted by a disinterested third party (D.S.) who had never previously contacted any of the patients and who will not be involved in their care in the future. Three patients were lost to follow-up review.

*Statistical Considerations*

Differences and relationships were analyzed using paired and unpaired t-tests, F-tests for simple linear regression, Pearson correlation coefficient and Spearman rank correlation analyses, and chi-square tests. Based on the previous reported use of PNS, institutional review board approval for this study was deemed unnecessary.

## Results

*Patient Population*

Of 32 patients eligible for this study, two patients failed to achieve significant improvement with Stage I screening. The remaining 30 patients (94%) underwent placement of the permanent generator and extension wire. The preimplantation characteristics of these patients are shown in Table 1. The length of prestimulator symptoms varied from 4 months to 8 years (2.6 ± 0.4 years, mean ± standard error of the mean). There was a statistically significant predominance of women in this study (21 of 30, $p < 0.05$). Electrodes were distributed as follows: median, seven; ulnar, 10; radial, one; common peroneal, five; and posterior tibial, seven patients. Outcome measures at 1 month after stimulator placement and at last follow up are described in Tables 1 and 2. Descriptive analyses of key measures are shown in Table 3.

*Patient Successes*

Overall, 19 (63%) of 30 patients experienced good or fair relief on a consistent basis. The cumulative long-term success rate is shown by a Kaplan–Meyer analysis (Fig. 1) in which survival or "success" is defined as a rating of good or fair, and death or "failure" is defined as poor or no pain relief. The analysis indicates that most of the failures occurred in the first 2 years. The 19 successful patients have been followed postimplantation for 2.2 ± 0.6 years (mean ± standard error of the mean). Ten had good long-term relief and nine had fair relief. Patients with a fair rating had a shorter follow-up time than patients with a good rating (2.4 ± 0.2 vs. 3.2 ± 0.2 years, $p < 0.01$). Of these Stage III patients, only one experienced a permanent reversal of the RSD symptoms to the point at which PNS was no longer required.

*Pain.* Pain reduction in these patients was dramatic; with a reduction from 8.3 ± 0.3 preimplantation to 3.5 ± 0.4 (56.7% ± 5.0% reduction) at the latest follow up ($p <$

TABLE 1

*Preimplantation characteristics and short-term follow up in 30 patients treated with peripheral nerve stimulation for reflex sympathetic dystrophy**

| Case No. | Affected Nerves: Initial† | VDS Preop | Physical Changes | | | Narcotics Preop | Non-narcotics Preop | Activity Preop‡ | Prior Treatments | Length of Symptoms Preop (yrs) | Age at Op | Date Stimulator Placed | Nerve Stimulated | 1-Mo Follow Up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Vaso-motor | Trophic | Motor | | | | | | | | | VDS | Physical Changes: Vaso-motor | Trophic | Motor |
| 1 | post tib (ipsilat com peron) | 7/10 | mild | min | mod | none | ibuprofen | 100 | symp, PT | 5.0 | 40 | 10/29/90 | post tib | 4/10 | none | mild | sev |
| 2 | ulnar (contralat ulnar) | 9/10 | mild | min | min | oxycodone | none | 80 | PT, inf | 1.5 | 36 | 11/14/90 | ulnar | 2/10 | none | min | min |
| 3 | median | 10/10 | mod | min | mild | codeine | ibuprofen | 80 | PT, stell | 0.5 | 63 | 11/26/90 | median | 1/10 | none | min | mild |
| 4 | ulnar | 10/10 | mod | min | mild | oxycodone | none | 70 | stell, ul block | 1.5 | 24 | 12/10/90 | ulnar | 6/10 | none | min | mild |
| 5 | median (ipsilat ulnar) | 8/10 | sev | mod | mod | oxycodone | none | 30 | PT, inf, stell | 0.3 | 27 | 12/10/90 | median | 1/10 | mild | mod | mild |
| 6 | com peron (ipsilat post tib) | 7/10 | mod | min | min | none | naproxin | 70 | PT, inf | 1.5 | 51 | 12/18/90 | com peron | 3/10 | min | min | min |
| 7 | median | 8/10 | mod | mild | mild | oxycodone | none | 70 | PT, stell | 1.0 | 35 | 12/18/90 | median | 5/10 | mild | mild | mild |
| 8 | com peron | 9/10 | mod | mild | mild | codeine | none | 70 | PT, inf | 1.5 | 24 | 2/8/91 | com peron | 4/10 | min | mild | mild |
| 9 | ulnar | 9/10 | mod | min | mild | none | naproxin | 30 | PT, inf, stell | 1.0 | 35 | 3/26/91 | ulnar | 6/10 | none | min | mild |
| 10 | median (contralat median) | 7/10 | mod | mod | mod | fentanyl | ketorolac | 30 | PT, inf, stell | 6.0 | 42 | 4/3/91 | median | 2/10 | min | mod | mod |
| 11 | ulnar (ipsilat median) | 9/10 | mod | min | mod | morphine | none | 60 | PT, stell | 1.0 | 32 | 4/29/91 | ulnar | 7/10 | min | min | mod |
| 12 | post tib | 8/10 | mod | min | mild | propoxyphene | none | 90 | PT, symp | 5.0 | 52 | 5/29/91 | post tib | 6/10 | none | min | min |
| 13 | com peron | 8/10 | mod | mild | mild | oxycodone | none | 70 | PT, symp | 2.0 | 31 | 5/31/91 | com peron | 5/10 | mild | mild | mild |
| 14 | median | 8/10 | mod | min | mild | none | ibuprofen | 30 | PT, stell | 4.0 | 34 | 6/4/91 | median | 3/10 | min | min | mild |
| 15 | post tib | 6/10 | mod | min | mod | codeine | none | 90 | PT, symp | 0.5 | 14 | 6/6/91 | post tib | 4/10 | none | min | mod |
| 16 | com peron | 8/10 | mod | min | mild | none | ibuprofen | 80 | PT, symp | 1.5 | 38 | 6/24/91 | com peron | 6/10 | min | min | mild |
| 17 | post tib | 7/10 | mod | min | min | propoxyphene | none | 100 | PT, inf | 6.0 | 20 | 6/24/91 | post tib | 3/10 | none | min | min |
| 18 | ulnar | 8/10 | mild | mild | mild | oxycodone | none | 80 | PT, stell | 1.0 | 50 | 7/30/91 | ulnar | 5/10 | min | mild | mild |
| 19 | post tib (ipsilat com peron) | 9/10 | mod | mild | mod | hydrocodone | none | 70 | PT, symp | 1.5 | 34 | 9/1/89 | post tib | 6/10 | mild | mild | mod |
| 20 | post tib (contralat post tib) | 8/10 | mod | mild | mod | codeine | none | 100 | PT, inf, symp | 8.0 | 46 | 9/18/91 | post tib | 1/10 | min | mild | mod |
| 21 | ulnar | 6/10 | mild | min | mild | oxycodone | none | 100 | PT | 4.0 | 30 | 11/19/91 | ulnar | 3/10 | none | min | mild |
| 22 | ulnar | 9/10 | sev | mod | mod | hydrocodone | none | 80 | PT, inf, stell | 2.5 | 30 | 5/23/91 | ulnar | 6/10 | mild | mod | mod |
| 23 | ulnar (ipsilat median) | 9/10 | sev | mod | mod | oxycodone | ibuprofen | 70 | PT, inf, stell | 3.0 | 27 | 9/18/91 | ulnar | 5/10 | mild | mod | mod |
| 24 | com peron | 8/10 | mod | min | mild | codeine | none | 70 | PT, symp | 0.8 | 35 | 2/25/92 | com peron | 2/10 | mild | min | mild |
| 25 | ulnar | 9/10 | mod | min | mild | oxycodone | none | 80 | PT, stell | 7.0 | 31 | 3/31/92 | ulnar | 3/10 | min | min | mild |
| 26 | median (ipsilat ulnar) | 7/10 | mod | min | mild | morphine | none | 80 | PT | 3.0 | 37 | 6/16/92 | median | 5/10 | min | min | mild |
| 27 | ulnar (ipsilat median) | 6/10 | mod | mild | min | oxycodone | ibuprofen | 80 | PT, stell | 3.0 | 46 | 6/23/92 | ulnar | 4/10 | mild | mild | min |
| 28 | radial | 10/10 | mod | min | mild | hydrocodone | none | 70 | PT | 0.8 | 46 | 8/4/92 | radial | 2/10 | none | min | mild |
| 29 | median (ipsilat ulnar) | 9/10 | mild | mild | min | fentanyl | ibuprofen | 80 | PT | 4.0 | 60 | 8/18/92 | median | 6/10 | min | mild | min |
| 30 | post tib (contralat post tib) | 8/10 | mod | min | min | fentanyl | none | 20 | PT | 1.0 | 46 | 10/13/92 | post tib | 5/10 | min | min | min |

* Abbreviations: com peron = common peroneal; inf = epidural spinal infusion for 1 to 3 months; min = minimal; mod = moderate; post tib = posterior tibial; PT = physical therapy; sev = severe; stell = stellate ganglion block; symp = sympathetic block; ul block = ulnar nerve block; VDS = average verbal digital scale pain rating (see text for method).

† Secondarily affected nerve shown in parentheses.

‡ Activity rating: 100 = full-time job; 90 = part-time job; 80 = drives a car ≥1 time per month; 70 = out of house and property ≥2 times per month; 60 = out of house and property <2 times per month; 50 = out of house but not off property; 40 = does household chores; 30 = no household chores but out of bed ≥6 hrs per day; 20 = out of bed <6 hrs per day; 10 = bedbound; 0 = dead.

TABLE 2

*Outcome in 30 patients treated with peripheral nerve stimulation for reflex sympathetic dystrophy**

| Case No. | Reoperations | | | | Length Follow Up (yrs)† | VDS Last Follow Up | Physical Changes | | | Narcotic Use Last Follow Up | Nonnarcotic Use Last Follow Up | Spread of Symptoms & Changes | Activity Last Follow Up | Status Last Follow Up‡ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st | 2nd | 3rd | 4th | | | Vaso-motor | Trophic | Motor | | | | | |
| 1 | 3/14/91; ipsilat com peron elect | 1/7/93; remove stim | none | none | 2.2 | 8/10 | mild | mild | mod | codeine | ibuprofen | diffuse leg | 100 | no relief |
| 2 | 5/14/92; remove stim | none | none | none | 1.5 | 7/10 | mod | min | min | oxycodone | none | shoulder, chest | 80 | poor relief |
| 3 | none | none | none | none | 3.7 | 1/10 | none | none | min | none | none | none | 100 | good relief |
| 4 | none | none | none | none | 3.7 | 5/10 | min | none | min | none | none | none | 80 | good relief |
| 5 | 4/1/91; ipsilat ulnar elect | 3/31/92; spinal elect | 12/11/92; revise ulnar elect | none | 3.7 | 2/10 | mild | mild | min | none | none | shoulder, chest, contralat arm | 90 | good relief |
| 6 | 6/12/91; revise com peron elect | none | none | none | 1.0 | 7/10 | mod | min | mod | propoxy-phene | naprosyn | diffuse leg | 70 | no relief |
| 7 | none | none | none | none | 2.3 | 3/10 | mod | mild | mild | none | ibuprofen | none | 80 | fair relief |
| 8 | none | none | none | none | 2.3 | 5/10 | min | min | none | none | acetamino-phen | none | 80 | fair relief |
| 9 | 5/13/91; revise extension | 1/23/92; revise ulnar elect | none | none | 3.4 | 2/10 | min | none | min | none | none | none | 90 | good relief |
| 10 | 2/7/92; contralat median elect | 2/27/92; revise contra-lat median elect | 10/6/92; revise contra-lat median elect | 12/3/92; revise extension | 3.4 | 2/10 | min | min | min | none | none | none | 80 | good relief |
| 11 | 7/2/91; ipsilat median elect | none | none | none | 1.3 | 5/10 | mod | min | mod | morphine | none | diffuse arm, chest, legs | 80 | poor relief |
| 12 | none | none | none | none | 3.2 | 6/10 | min | none | min | none | nabumetone | none | 100 | fair relief |
| 13 | none | none | none | none | 0.8 | 7/10 | mild | mild | mild | oxycodone | none | diffuse leg | 70 | poor relief |
| 14 | none | none | none | none | 3.2 | 1/10 | min | none | min | none | none | none | 80 | good relief |
| 15 | none | none | none | none | 3.2 | 4/10 | min | none | mild | none | acetamino-phen | none | 100 | fair relief |
| 16 | none | none | none | none | 0.9 | 8/10 | mod | mild | mild | none | ibuprofen | none | 80 | no relief |
| 17 | 12/23/91; revise post tib elect | none | none | none | 3.1 | 2/10 | min | none | none | none | ibuprofen | none | 100 | good relief |
| 18 | none | none | none | none | 3.0 | 3/10 | min | none | mild | none | none | none | 100 | good relief |
| 19 | 3/26/91; revise post tib elect | 8/13/91; revise post tib elect | none | none | 1.9 | 7/10 | mod | mild | mod | hydrocodone | none | diffuse leg | 70 | poor relief |
| 20 | 8/11/92; contralat post tib elect | none | none | none | 2.9 | 2/10 | min | min | mild | hydrocodone | none | contralat leg | 100 | good relief |
| 21 | none | none | none | none | 2.8 | 4/10 | none | none | min | none | none | none | 100 | fair relief |
| 22 | 2/26/91; revise ulnar elect | 5/23/91; revise ulnar elect | none | none | 1.9 | 6/10 | min | min | mild | codeine | ibuprofen | diffuse arm | 80 | fair relief |
| 23 | 2/21/92; ipsilat median elect | 10/8/92; revise ulnar elect | none | none | 1.1 | 9/10 | mod | mod | mod | oxycodone | ibuprofen | shoulder, diffuse arm | 70 | poor relief |
| 24 | none | none | none | none | 0.8 | 8/10 | mod | mild | mild | oxycodone | none | diffuse both legs | 70 | no relief |
| 25 | 6/12/92; revise generator | none | none | none | 2.4 | 6/10 | min | min | min | oxycodone | none | none | 100 | fair relief |
| 26 | none | none | none | none | 1.0 | 5/10 | mod | min | mild | none | none | diffuse arm | 80 | poor relief |
| 27 | 6/27/92; revise generator | none | none | none | 1.3 | 6/10 | mod | mild | min | hydrocodone, meperidine | none | diffuse arm | 80 | no relief |
| 28 | none | none | none | none | 2.0 | 3/10 | none | none | min | none | none | none | 100 | good relief |
| 29 | none | none | none | none | 2.0 | 4/10 | mild | mild | mild | none | ibuprofen | none | 80 | fair relief |
| 30 | none | none | none | none | 1.8 | 6/10 | min | none | none | methadone, morphine | none | shoulder, neck, eyes, legs | 80 | fair relief |

* Abbreviations: elect = electrode; spinal = spinal cord stimulator electrode; stim = stimulator generator. For other abbreviations and activity rating, see Table 1.
† Length of follow up (good to fair relief patients) or time to failure (poor or no pain relief patients).
‡ See *Follow-up Evaluation* for rating criteria.

TABLE 3

*Summary of treatment results of peripheral nerve stimulation**

| Parameter | Long-Term Success (mean ± SEM) (19 patients) | Long-Term Failure (mean ± SEM) (11 patients) |
|---|---|---|
| VDS pain score | | |
| preop | 8.3 ± 0.3 | 7.9 ± 0.3 |
| 1 mo postop (% change)† | 3.8 ± 0.4 | 4.5 ± 0.5 |
| | (53.6% ± 5.1%) | (43.4% ± 6.0%) |
| | p < 0.001‡ | p < 0.001‡ |
| last follow up (% change)† | 3.5 ± 0.4 | 7.0 ± 0.4 |
| | (56.7% ± 5.0%) | (10.5% ± 5.4%) |
| | p < 0.001‡ | p < 0.001§ |
| oral analgesics‖ | | |
| preop | 2.4 ± 0.2 | 2.3 ± 0.3 |
| last follow up | 0.8 ± 0.2 | 2.3 ± 0.3 |
| activity rating** | | |
| preop | 68.9 ± 6.3 | 75.5 ± 3.3 |
| last follow up (% change)† | 90.5 ± 2.3 | 77.3 ± 2.9 |
| | (63.3% ± 21.8%) | (3.0% ± 3.2%) |
| age at stimulator placement (yrs) | 37.2 ± 3.2 | 37.4 ± 2.0 |
| length of symptoms preimplant (yrs) | 2.9 ± 0.6 | 2.2 ± 0.4 |
| length follow up or time to failure (yrs) | | |
| all patients | 2.8 ± 0.1 | 1.3 ± 0.1 |
| good rating | 3.2 ± 0.2 | NA |
| fair rating | 2.4 ± 0.2 | NA |
| | p < 0.01 | |
| patient assessment of pain reduction†† | 60.9% ± 5.7% | NA |

* Abbreviations: NA = not applicable; SEM = standard error of the mean; VDS = verbal digital scale.

† Percent change as compared to preoperative value.

‡ Statistically significant as compared to preoperative value.

§ Statistically significant as compared to corresponding value in long-term success group.

‖ Rated on following scale: 3 = Schedule 2 (± nonnarcotic) analgesics; 2 = Schedule 3 (± nonnarcotic) analgesics; 1 = nonnarcotic analgesics only; 0 = no oral analgesics.

** Rated on same scale as in Tables 1 and 2.

†† As compared to good rating for success group.

0.001). Relative components of mechanical allodynia versus spontaneous deep pain were equal in these patients, both preimplantation and at last follow up. When questioned at follow up about degree of pain compared to preimplant levels, patients estimated a pain reduction of 60.9% ± 5.7%. A linear relationship was observed between change in verbal digital scale pain scores (1 −[verbal digital scale at follow up/verbal digital scale preimplant], expressed as a percentage) and patient estimate of pain reduction ($p < 0.001$, Fig. 2).

*Physical Examination Changes.* Changes in vasomotor tone were improved markedly but improvements in motor weakness and trophic changes were less impressive. The improvement in motor weakness was directly related to the amount of physical therapy that was received after the operation. In almost all patients, a dramatic improvement in pain and vasomotor changes was noted for 4 to 6 weeks. After that time there was a decay, although never to the degree that had been experienced before stimulator placement. This "sag" period generally lasted 2 to 3 months, after which a gradual improvement continued to a final plateau at approximately 1 year postimplantation.

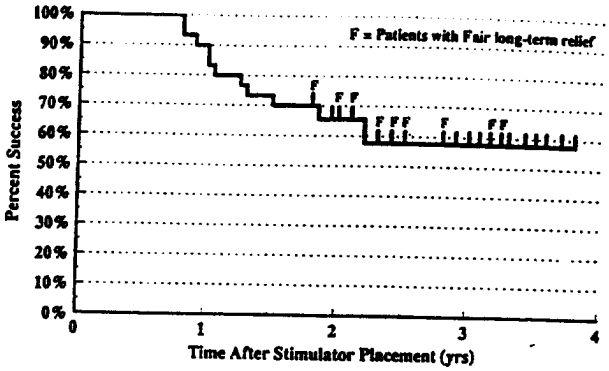


FIG. 1. Graph showing Kaplan–Meier analysis of patient outcome in which success is a final good or fair rating and failure is a poor or no relief rating (see text for criteria). The tick marks or "blips" on the line indicate length of follow up at last evaluation for successful patients. Down steps in the line indicate follow-up times at which individual patients became treatment failures.

*Activity.* Activity levels (see Table 1 footnote) increased by 63.3% ± 21.8% in the success group between preimplantation and last follow-up evaluations (from 68.9 ± 6.3 to 90.5 ± 2.3, $p < 0.001$) but not for the failure group. Four of the successful patients increased employment levels from unemployed prestimulator to full-time employment, two from unemployed to part-time employment, and two from part-time to full-time employment. Three patients were working full-time before and after stimulator placement and eight patients were unemployed before and after placement.

Patients resuming part-time or full-time work had not worked for 1.7 ± 1.0 years as compared to 3.6 ± 1.3 years for those continuing not to work. This difference was not statistically significant. One patient, who had been totally unemployed for 7 years before stimulator placement, returned to full-time work. Daily activities in which the successful patients showed improvement were working, sleeping, motor strength, and driving a car (Fig. 3). Of the

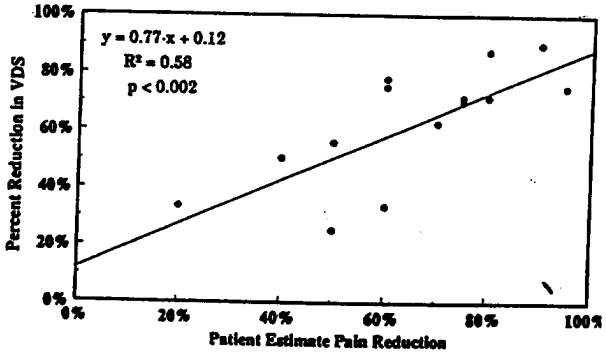


FIG. 2. Scatterplot showing relationship in successful patients between percent reduction in verbal digital scale (VDS) scores for pain and patient estimate of pain reduction in follow up by third party. Percentages are based on status at last follow up as compared to preimplant status. Statistical significance and linear relationship between variables are shown.

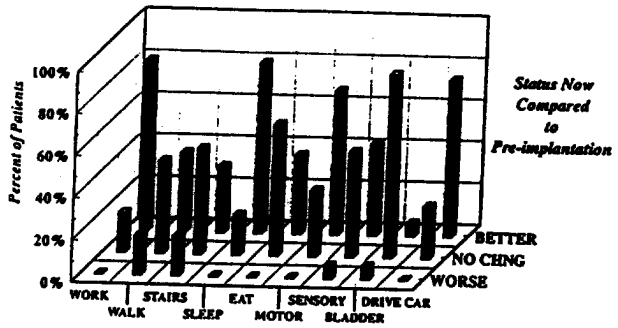


FIG. 3. Bar graph showing status at last follow up, as compared to preimplantation status, of daily activities for successful patients. Data obtained by disinterested third party follow up.

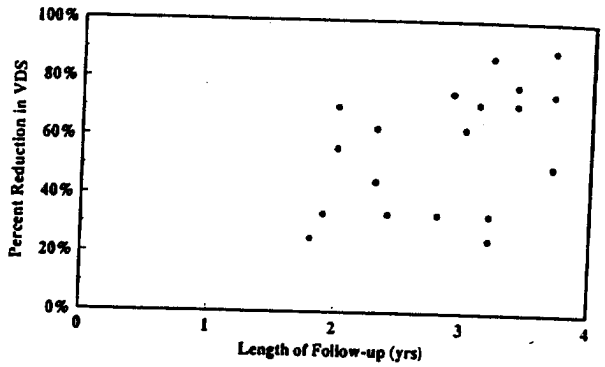


FIG. 4. Scatterplot showing relationship in successful patients between percent reduction in verbal digital scale (VDS) scores and length of follow up after stimulator placement. Although not linear, a significant relationship ($p < 0.05$) was found between the two variables.

successful patients, all but one stated in the follow-up survey that they would have the stimulator placed again.

*Stimulator Settings.* During long-term follow up of 1 to 3 years, the stimulator voltages remained virtually unchanged. In general, PNS has provided an excellent stimulation pattern in relation to the pain pattern although one notable exception is that, in many patients, it has been difficult to match elbow pain from the ulnar nerve with electrical stimulation to the same nerve.

*Parameter Relationships.* A nonlinear association (Fig. 4) was found between length of follow up and reduction in verbal digital pain scale (last follow up as compared to preimplant, $p < 0.05$). There was no significant relationship between changes in activity levels and the following parameters: 1) length of follow up; 2) pain reduction; or 3) improvement in physical findings. There was no difference in length of symptoms before stimulator placement between the success and failure groups or, within the success group, between the good and fair patients. No relationships were found between individual activities and other parameters such as pain reduction, increased activity, or oral analgesic use.

### *Patient Failures*

Failure of long-term pain relief occurred in 11 patients at $1.3 \pm 0.1$ years. There were significant reductions ($p < 0.001$) in pain ratings for the failure group from preimplantation to 1 month postimplantation ($43.4\% \pm 6.0\%$), but pain ratings at last follow up were essentially the same as preimplantation levels. There was no significant improvement in vasomotor tone changes, trophic changes, or somatic motor weakness in the failure group. Activity levels showed almost no change between the preimplantation and the last follow-up evaluations.

### *Placement of Additional Electrodes*

Of the 13 patients who had RSD symptoms and findings in the distribution of more than one major peripheral nerve before placement, six (46%) later required a second electrode placement. Each of these additional electrodes was connected to a separate permanent extension wire and implanted generator. Approximately half of these additional electrodes were placed in the same limb as the initial electrode (for example, initial median electrode followed by an ulnar electrode) and half in the contralateral limb (for example, initial electrode on the right median nerve followed by an electrode on the left median nerve).

The second electrodes were placed $27.4 \pm 11.7$ months after the first electrode when it became apparent that there were significant improvements in the distribution of the first electrode but worsened or unimproved symptoms outside this distribution. Three of the five patients in the success group who had involvement of more than one nerve had good pain relief and, perhaps related to this, these three represent the only patients who received a second electrode in the success group. Initial involvement of more than one major peripheral nerve (five of 19 success group patients, eight of 11 failure group patients) correlated closely with a final poor or no relief rating ($p < 0.01$).

### *Complications and Modifications of Operative Technique*

Of the 30 patients who were implanted with permanent PNS systems, eight (27%) later required a revision of the electrode (Table 4). Ulnar revisions were related to difficulties in obtaining and maintaining a good pattern of stimulation around the medial epicondyle of the elbow. For cosmetic reasons, the generators in some patients were located in the midaxillary line rather than the infraclavicular fossa. These generators came loose from anchoring sutures in two patients and were revised for cosmetic reasons in two patients. There was no incidence of wound or hardware infection.

For patients with pain located mainly in the distribution of the medial or lateral plantar nerve, the placement of a posterior tibial electrode is now performed using local anesthetic with intravenous sedation. This allows testing of the electrode intraoperatively in different locations around the nerve so that an optimum pattern in the appropriate plantar nerve can be obtained. For common peroneal stimulation, the electrode is now placed more proximally, just under the biceps femoris tendon/muscle to avoid electrode dislodgement at the joint. When generators are placed in the midaxillary line, redundant extension wire is provided and frequent abduction exercises prescribed to prevent later tethering of the wire.

TABLE 4

*Technical problems experienced by 30 patients undergoing electrode placement for relief of RSD**

| Factor | Success Group (%) | Failure Group (%) |
|---|---|---|
| no problem | 12 (63) | 4 (36) |
| additional electrode | 3 (16) | 3 (27) |
| revision of electrode | 5 (26) | 3 (27) |
| revision of extension wire | 2 (11) | 0 (0) |
| revision of generator | 1 (5) | 1 (9) |
| removal of generator | 1 (5)† | 2 (18) |
| total‡ | 19 | 11 |

* Abbreviation: RSD = reflex sympathetic dystrophy.

† In Case 9, the generator was no longer required because of long-term reversal of RSD and was removed to permit patient to undergo magnetic resonance imaging of spine.

‡ Some patients experienced more than one complication.

## Discussion

### *Reflex Sympathetic Dystrophy*

The classification of chronic pain syndromes by the International Association for the Study of Pain in 1986 defined RSD as "continuous pain in a portion of an extremity after trauma which may include fracture but does not involve a major nerve, associated with sympathetic hyperactivity."[20] More recently, the terminology has been changed to Complex Regional Pain Syndrome (CRPS) with the basic definition: "a syndrome that develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is disproportionate to the inciting event. It is associated at some point with evidence of edema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, or allodynia or hyperalgesia."[21,34] Type II CRPS, which corresponds to causalgia, has additional criteria of "burning pain, allodynia, and hyperpathia usually in the hand or foot after partial injury of a nerve or one of its major branches." The new terminology was developed at a special consensus workshop held in October, 1993, that involved anesthesiologists, neurologists, neurosurgeons, psychiatrists, neuroscientists, and internists. The workshop examined the diagnosis of RSD, causalgia, and sympathetically maintained pain and attempted to better define the various symptoms and findings associated with the disorders. The terminology for CRPS has been adopted in the most recent International Association for the Study of Pain classification of chronic pain. Most patients in the present study had some form of initial trauma, although not major trauma, and might be considered CRPS Type II.

A three-level staging system has been developed to describe the severity of the clinical disorder.[2] Stage I includes patients with mild pain and only vasomotor changes. Stage II represents patients in whom the pain and vasomotor changes are more severe and who have minimal motor weakness. Stage III includes severe pain, moderate to marked vasomotor changes, moderate motor weakness, and objective trophic changes. Clinical Stage III together with symptom duration greater than 1 year are considered poor prognostic factors. All of the patients in this study had trophic changes, and 25 (83%) of 30 patients had symptoms for more than 1 year prior to the placement of a stimulator. The predominance of women in the present study is unexplained although it might reflect an undetermined referral bias; other reports have shown a higher proportion of men.[6,15]

Perhaps because of a poor understanding of the diagnosis or treatment of this disease, many of the Stage III patients in this study had symptoms for more than 1 year before interventional therapy. Given the better success rates in Stage I or II patients and the tendency of these patients to progress to a Stage III condition within 6 to 12 months if not completely treated,[38] early, aggressive, multidisciplinary therapy for RSD patients is important.[28] In the present study, however, no consistent relationship was seen between treatment failure and duration of symptoms.

Evidence suggests that the origin of RSD symptoms might be at peripheral, spinal cord, and/or dorsal root ganglion (DRG) levels. At the peripheral level, α-adrenoreceptors in veins as well as peripheral skin C-fiber nociceptors and mechanoreceptors have been found to exhibit an increased responsiveness to local infusions of noradrenaline.[18,29,33] It is unclear whether this occurs as an increased sensitivity of the postsynaptic receptor or decreased reuptake of noradrenaline presynaptically. At the spinal level, there is evidence that nociceptive afferent impulses, including high threshold afferent inputs, maintain altered central processing or sensitization. This process might involve *N*-methyl-D-aspartate (NMDA) receptors, and blockage of the peripheral input can allow the central processing to return to normal.[9,39] In abnormal states, stimulation in the DRG of postganglionic sympathetic efferents can cause or augment afferent discharge from 50% or more of the DRG sensory neurons ("sympathetic-sensory coupling").[8,13,19] There can also be "crossed afterdischarges" in which excitation of specific afferent neurons in the DRG can excite neighboring afferent neurons.

### *Treatment of Reflex Sympathetic Dystrophy*

The treatment of RSD usually requires a multifaceted approach involving aggressive physical therapy, especially stress-loading exercise, coupled with various medications. Stress-loading exercise involves active traction and compression exercises that provide stressful stimuli to the affected extremity without joint motion. The goal is to eliminate contractures and fibrosis in affected muscles and tendons, and this can be effective even without other therapy, especially in Stage I or II patients.[7,37] Local effects include increasing blood flow to tissues and stimulation of myelinated and unmyelinated afferents, especially high-threshold mechanoreceptors.[12]

Approximately 15% to 16% of all patients with RSD might not respond to various medications and therapies. For this subset, blocks, intravenous or regional infusions, and/or transcutaneous electrical nerve stimulation are frequently successful on a second level of the treatment ladder.[14,32] These various treatment combinations can be effective in Stage I or II patients, but have a lower success rate in Stage III patients.

Sympathectomy has been helpful in the treatment of pain associated with major causalgia in 12% to 97% of patients. Complete surgical sympathectomy is important for the best results, but persistent mild hyperpathia, tenderness, joint stiffness, and trophic changes have been

noted in 30% to 40% of patients.[10,35] Partial or complete regrowth of sympathetic fibers can also occur.[10] Although sympathectomy can be helpful in treatment of sympathetic hyperfunction, pain relief in RSD, as contrasted to major causalgia, is unpredictable.[36] The relative roles of surgical sympathectomy and stimulation, either spinal or peripheral, are unknown. A future study involving a direct comparison of ablative versus augmentative procedures for the patient population represented in this study would be most useful.

Compared to other chronic pain conditions, RSD appears to be less responsive, or even unresponsive to intraspinal opioids.[22] The long-term intraspinal infusion of an $\alpha_2$-adrenergic agonist such as clonidine hydrochloride is a promising option although the clinical availability of a spinal drug preparation in the United States is 1 to 2 years away.[30]

Spinal cord stimulation has been the major therapeutic option available for patients with severe RSD.[1,4,31] It is an effective modality although success depends on producing a pattern of perceived stimulation that matches the area of vasomotor changes and the area of mechanical allodynia and spontaneous, deep pain. The overall success rate in the treatment of severe RSD has been reported to be from 50% to 80% with the advantage of a percutaneous placement technique.

*History of Peripheral Nerve Stimulation*

Electrical stimulation applied to peripheral nerves was first developed in approximately 1969.[5,17] The original electrodes often were cuff shaped and the results were encouraging but limited.[5,16,17] Interest in the use of PNS was renewed in the late 1980s with the application of flat or oval-shaped electrode templates that contained four electrode contacts.[24,25,27] The presence of four electrode contacts, coupled with the availability of implantable, programmable low-voltage generators, provided greater ability to deliver consistent and evenly distributed stimulation to a peripheral nerve, although well-analyzed studies were absent.

The mechanisms of action for both PNS and SCS in the treatment of RSD remain unclear and might be different for these two modalities. The voltage level for PNS, however, probably activates only large myelinated fibers.[26] Recordings from peripheral stimulator electrodes have shown spontaneous abnormal discharges in the affected nerve.[26] Constant peripheral stimulation might provide a consistent blockade of afferent peripheral input, allowing central processing to return to normal. Alternatively, afferent impulses from electrical stimulation of the nerve might block, at the spinal cord level, other abnormal nociceptive inputs in a gate-control manner. Based on previous reports,[24–27] constant stimulation was used for peripheral stimulation in this study. Because the nervous system often responds better to variation, a future study examining the relative benefits of constant versus intermittent stimulation seems indicated.

*Efficacy of Peripheral Nervous System*

The present study indicates that PNS can provide good relief of RSD symptoms and findings over a period of 1 to 4 years. This study indicates that overall 63% of all patients experienced good or fair relief, that the majority of the successful patients have been followed for long periods of time, and that most of the failures occurred in the first 2 years after stimulator placement (Fig. 1). Considering that these were Stage III patients who have failed to obtain long-term relief with almost every other modality, except a trial of SCS, the overall success of 63% is very encouraging.

*Difficult Patients and Complications*

The observation that most of the failures occurred in the first 2 years postimplantation provides further support for the importance of breaking the vicious cycle of RSD on a medium-term basis to obtain long-term relief. Establishing an adequate pattern of stimulation was more difficult in patients with pain and vasomotor changes in the area of the ulnar nerve at the medial epicondyle of the elbow. Patients with RSD symptoms and findings partly in the distribution of a second major peripheral nerve territory also were more difficult to treat.

For pain in the medial or lateral plantar nerve distribution, the electrode was placed using local anesthesia and intravenous sedation, with intraoperative testing of the electrode in different locations around the tibial nerve. For generator placement in the midaxillary line at the level of the nipple, tethering of the extension wire in the area of the anterior axillary fold has been eliminated by starting full abduction exercises of the arm immediately after the operation. The use of a free fascial cover for the electrode did not produce any more scarring but did allow greater ease of electrode placement. Delayed electrode movement was reduced by placing the electrode under or beside the nerve.

*Relative Roles of SCS and PNS*

The relative roles of SCS and PNS in the treatment of these patients remains unclear. This study was not designed to provide information about the relative roles of PNS and SCS in the treatment of these refractory patients, but we do know that epidural placement, especially using a percutaneously placed electrode, can result in delayed electrode movement and an inadequate stimulation pattern. With SCS, it can be difficult to match patterns of perceived electrical stimulation to some pain patterns, especially those involving only a specific part of the hand or foot. However, these same areas often correlate well with the distribution of a major peripheral nerve.

Severe RSD will frequently start at a focal point but then spread to involve other limbs, and can become an almost systemic disease. Because SCS provides more generalized coverage than PNS, it could be more advantageous in severe RSD where symptoms have spread to other limbs. Aggressive treatment of the starting point, however, can provide permanent relief in the original limb and also in these secondary areas of involvement, although the mechanism for these distant effects is unclear. In this study, PNS was applied to some patients with symptoms beyond the distribution of one major peripheral nerve and, in fact, was effective in some but not all patients for pain and symptom reduction in areas outside the stimulated nerve.

*Future Study and Treatments*

The best application of PNS, at least on the basis of this study, appears to be for a relatively small group of patients

with RSD pain and clinical findings localized in the distribution of only one major peripheral nerve. Whereas SCS can also be effective in the treatment of RSD, any comparison of the relative effective rates for SCS and PNS will have to await a formal, randomized, comparative study of the two modalities in the treatment of severe RSD. Intraspinal infusions of nonopioid agents such as the $\alpha_2$-adrenergic agonist clonidine hydrochloride, or the NMDA antagonist dextromorphan, also seem to be promising future treatments.

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