Krishna Kumar, M.D.
Department of Neurosurgery,
Regina General Hospital,
Regina, Canada

Rod S. Taylor, Ph.D.
Peninsula Medical School,
Universities of Exeter and Plymouth,
Exeter, England

Line Jacques, M.D.
Department of Neurosurgery,
Montreal Neurological Institute
and Hospital,
Montreal, Canada

Sam Eldabe, M.D.
Department of Pain and Anaesthesia,
James Cook University Hospital,
Middlesbrough, England

Mario Meglio, M.D.
Department of Functional Neurosurgery,
Gemelli Catholic University Hospital,
Rome, Italy

Joan Molet, M.D., Ph.D.
Department of Neurosurgery,
Hospital Santa Creu I Sant Pau,
Barcelona, Spain

Simon Thomson, M.D.
Pain Clinic,
Basildon and Thurrock University Hospitals,
Basildon, England

Jim O'Callaghan, M.D.
Pain Clinic,
Axxon Pain Medicine,
Brisbane, Australia

Elon Eisenberg, M.D.
Pain Relief Unit,
Rambam Medical Centre,
Haifa, Israel

Germain Milbouw, M.D.
Neurosurgery,
Namur Regional Hospital,
Namur, Belgium

Eric Buchser, M.D.
Pain Clinic,
Morges Hospital,
Morges, Switzerland

Gianpaolo Fortini, M.D.
Pain Clinic,
Varese Regional Hospital
and Macchi Foundation,
Varese, Italy

Jonathan Richardson, M.D.
Department of Pain and Anesthesia,
Bradford Hospitals,
Bradford, England

Richard B. North, M.D.
LifeBridge Health
Brain & Spine Institute,
Baltimore, Maryland

Reprint requests:
Richard B. North, M.D.,
LifeBridge Health
Brain & Spine Institute,
Mirowski Office Building,
5051 Greenspring Avenue,
Baltimore, MD 21209.

Received, April 8, 2008.
Accepted, May 15, 2008.

THE EFFECTS OF SPINAL CORD STIMULATION IN NEUROPATHIC PAIN ARE SUSTAINED: A 24-MONTH FOLLOW-UP OF THE PROSPECTIVE RANDOMIZED CONTROLLED MULTICENTER TRIAL OF THE EFFECTIVENESS OF SPINAL CORD STIMULATION

OBJECTIVE: After randomizing 100 failed back surgery syndrome patients to receive spinal cord stimulation (SCS) plus conventional medical management (CMM) or CMM alone, the results of the 6-month Prospective Randomized Controlled Multicenter Trial of the Effectiveness of Spinal Cord Stimulation (i.e., PROCESS) showed that SCS offered superior pain relief, health-related quality of life, and functional capacity. Because the rate of crossover favoring SCS beyond 6 months would bias a long-term randomized group comparison, we present all outcomes in patients who continued SCS from randomization to 24 months and, for illustrative purposes, the primary outcome (>50% leg pain relief) per randomization and final treatment.

METHODS: Patients provided data on pain, quality of life, function, pain medication use, treatment satisfaction, and employment status. Investigators documented adverse events. Data analysis included inferential comparisons and multivariate regression analyses.

RESULTS: The 42 patients continuing SCS (of 52 randomized to SCS) reported significantly improved leg pain relief ($P < 0.0001$), quality of life ($P \leq 0.01$), and functional capacity ($P = 0.0002$); and 13 patients (31%) required a device-related surgical revision. At 24 months, of 46 of 52 patients randomized to SCS and 41 of 48 randomized to CMM who were available, the primary outcome was achieved by 17 (37%) randomized to SCS versus 1 (2%) to CMM ($P = 0.003$) and by 34 (47%) of 72 patients who received SCS as final treatment versus 1 (7%) of 15 for CMM ($P = 0.02$).

CONCLUSION: At 24 months of SCS treatment, selected failed back surgery syndrome patients reported sustained pain relief, clinically important improvements in functional capacity and health-related quality of life, and satisfaction with treatment.

KEY WORDS: Failed back surgery syndrome, Neuropathic pain, Neurostimulation, Radicular pain, Randomized controlled trial, Spinal cord stimulation

Neurosurgery 63:762–770, 2008 DOI: 10.1227/01.NEU.0000325731.46702.D9 www.neurosurgery-online.com

Between 10 and 40% of patients who have undergone lumbosacral spine surgery to alleviate pain instead experience persistent or recurrent chronic pain (21, 31), so-called "failed back surgery syndrome" (FBSS). FBSS is, thus, the most common cause of chronic neuropathic pain (5). Patients with FBSS also report disability and reduced health-related quality of life and incur high healthcare costs (2, 19).

To evaluate the benefit of adding spinal cord stimulation (SCS) to nonsurgical conventional

ABBREVIATIONS: CMM, conventional medical management; **FBSS**, failed back surgery syndrome; **PROCESS**, Prospective Randomized Controlled Multicenter Trial of the Effectiveness of Spinal Cord Stimulation; **SCS**, spinal cord stimulation

medical management (CMM) in FBSS patients, the PROCESS trial (Prospective Randomized Controlled Multicenter Trial of the Effectiveness of Spinal Cord Stimulation, ISRCTN 77527324) randomized 100 patients from April 2003 to June 2005 in a total of 12 centers in Europe, Canada, Australia, and Israel to receive SCS plus CMM (SCS group) or CMM alone (CMM group). The primary outcome was the proportion of patients achieving at least 50% relief of leg pain. Secondary outcomes were improvement in back pain, health-related quality of life, and functional capacity; changes in pain medication and nondrug pain therapy; patient satisfaction with treatment; work status; and incidence of complications and adverse effects. Details of the study design, participants, interventions, and the 12-month outcome assessment have been described in previous publications (14, 15, 17).

At 6 months, the SCS group reported significantly better pain relief and clinically important improvements in functional capacity and health-related quality of life ($P < 0.05$ for all analyses) compared with the CMM group (15). After 6 months, patients failing to achieve adequate pain relief in either group could request crossover to the alternative treatment upon physician approval. By 12 months, 5 patients who were randomized to SCS crossed to CMM, and 28 patients who were randomized to CMM crossed to SCS (15). At 12 months, 24% of patients who received an electrode (either during the screening trial or as a result of system implantation) experienced a device-related complication requiring surgical intervention (15).

Although a long-term comparison of the SCS and CMM groups in the PROCESS trial would be valuable (few neuropathic pain management clinical trials report long-term findings) (8, 9), the level and asymmetric nature of crossover beyond 6 months would bias the analysis. In this report, therefore, we present results for the 42 (of 52) patients randomized to SCS in the PROCESS trial who continued to use SCS at 24 months (Fig. 1). (The number of patients randomized to and remaining in the CMM group was deemed too small [n = 11] to undertake a companion analysis.) For illustrative purposes only, we also provide a "modified intention-to-treat" or "treated-as-intended" (15, 20, 21) and final treatment comparison of the primary outcome at 24 months for all randomized patients.

PATIENTS AND METHODS

Patients

The patients were aged 18 years or older and suffered from predominant radiating pain in the legs (in dermatomal segments L4 and/or L5 and/or S1), attributable to a documented history of nerve injury (i.e., root compression by herniated disc, compatible with the pain complaint), with or without associated less severe back pain. The intensity of leg pain was at least 50 mm on a visual analog scale (0 equaling no pain, 100 mm representing the worst possible pain) for at least 6 months after at least 1 anatomically successful surgery for a herniated disc. The neuropathic nature of the pain was confirmed according to the routine clinical practice of each investigator and included mapping the pain distribution, examining sensory/motor/reflex changes, and electromyography. Some of the eligible patients had undergone additional procedures, particularly repeat lumbar disc operations, laminectomies with or without foraminotomies, or spinal fusions.

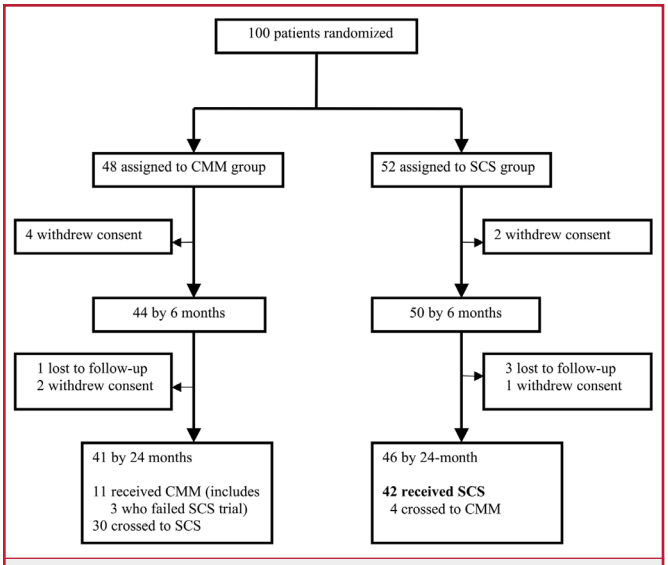

FIGURE 1. *Patient flow through trial to 24 months. SCS, spinal cord stimulation; CMM, conventional medical management.*

Exclusion criteria included the presence of another clinically significant or disabling chronic pain condition; an expected inability to receive or operate the SCS system; a history of a coagulation disorder, lupus erythematosus, diabetic neuropathy, rheumatoid arthritis, or ankylosing spondylitis; evidence of an active psychiatric disorder, any other condition known to affect the perception of pain, or an expected inability to evaluate treatment outcome; life expectancy of less than 1 year; or an existing or planned pregnancy.

All patients randomized to the SCS group underwent a screening trial. Those patients experiencing overlap of their pain with stimulation-induced paresthesia and at least 50% leg pain relief received an implantable neurostimulation system (Synergy system; Medtronic, Inc., Minneapolis, MN). Details of the implantation procedure have been described elsewhere (1).

Conventional Medical Management

At trial entry, the study investigators optimized the medication and nondrug therapy received by their patients according to local clinical practice. CMM included oral medication (i.e., opioids, nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants/antiepileptics, and other analgesic therapies), nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care. Invasive therapy, such as spinal surgery or implantation of an intrathecal drug delivery system, was not allowed.

Data Collection and Follow-up

Patients were assessed before randomization (baseline) and at 1, 3, 6, 9, 12, 18, and 24 months after initiation of treatment. Outcome data were gathered via patient self-report for leg and back pain, health-related quality of life (11, 18), functional capacity (7), changes in pain medication and nondrug pain therapy, patient satisfaction with treatment, and employment status. The investigators documented the nature and frequency of adverse events and complications.

Statistical Analysis

Results are reported as means and standard errors (for continuous outcomes) or proportions (for binary outcomes). Inferential comparison was performed between baseline and 24 months to account for the distribution and paired nature of the data. Pain is expressed as absolute values and as the proportion of patients who achieved at least 30 (6), 50, or 80% pain relief at follow-up. Opioid doses were converted to a morphine equivalent dose with the use of standard conversion tables (23, 26), and "low" and "high" morphine equivalent doses were calculated. For illustrative purposes, the primary outcome (≥50% leg pain relief) was compared for the SCS and CMM groups as randomized with crossovers who received the alternative therapy considered failures (i.e., "modified intention-to-treat" or "treated-as-intended") (15, 20, 21) and according to final treatment. Multivariate regression analyses adjusted for baseline covariates based on their contribution ($P < 0.1$) in stepwise regression.

Complications and adverse events are reported descriptively (10). Time to first surgical revision for patients experiencing a device-related complication was plotted with a Kaplan-Meier curve. All statistical analyses were conducted with SAS software (version 9.1; SAS Institute, Cary, NC).

RESULTS

Outcomes in Patients Randomized to and Continuing SCS

As shown in Figure 1, of 52 patients randomized to SCS, 42 were receiving stimulation at 24 months. The remaining 10 patients either crossed to CMM (n = 4), were lost to follow-up (n = 3), or withdrew consent (n = 3). With the exception of a slightly greater leg pain visual analog scale score ($P = 0.07$), the baseline characteristics of the 42 patients receiving SCS at 24 months were similar to those of the 10 patients who were not (Table 1).

Compared with baseline, at 24 months, the 42 patients experienced lower levels of leg pain ($P < 0.0001$) (Fig. 2A) but no significant difference in back pain ($P = 0.21$) (Fig. 2B). Patients also reported superior functional capacity on the Oswestry Disability Index ($P = 0.0002$) (Fig. 2C) and enhanced health-related quality of life on 7 of 8 dimensions of the Short-Form Health Survey-36 ($P \leq 0.01$, $P = 0.11$ for role emotional) (Fig. 2D) and according to the EuroQoL 5 days instrument ($P < 0.0001$) (Fig. 2E). As Table 2 indicates, neither analgesic drug intake nor nondrug therapy showed a clear pattern of change.

Of the 42 patients, 19 (45%) experienced a total of 34 SCS-related complications. The most frequent were electrode migration (14%), loss of paresthesia (12%), pain at the implanted pulse generator incision site (12%), and infection or wound breakdown (10%). For 13 patients (31%), surgical revision was required to resolve the event (Fig. 3; Table 3). Most (79%) of the revisions occurred in the first 12 months. In addition, 13 patients (31%) experienced at least one non-SCS-related event associated with their FBSS (Table 4). Patient satisfaction was high, with 93% at 24 months declaring that based on their experience so far, they would have agreed to treatment (Table 2). Of those patients who underwent a surgical revision for an SCS-related complication, 89% were satisfied with SCS therapy.

Of the 42 patients, 37 were of working age, and 5 were older than 65 years of age and did not work throughout the study period. At baseline, 9 patients were working, and 27 of the remaining 33 attributed their unemployment to pain and had been unemployed for a median of 2.76 years. At 24 months, 6 of the 9 continued to work, and an additional 5 of 33 returned to work; thus, 11 patients were working at the end of 2 years compared with 9 at baseline (Table 2). Among the 5 patients who returned to work at 24 months, 4 had been off work at baseline for 0.79, 1.9, 2.8, and 5.1 years (mean, 2.65 years; median, 2.35 years).

Illustrative Analyses: SCS versus CMM Groups

At 24 months, 46 of the 52 patients randomized to SCS and 41 of the 48 patients randomized to CMM were available for follow-up (Fig. 1). In the "modified intention-to-treat" or "treated-as-intended" analysis (outcomes assigned to randomized group with crossover considered a failure), 17 SCS patients

TABLE 1. Baseline characteristics of patients randomized to spinal cord stimulation[a]

	Continuing SCS at 24 mo (n = 42)	No SCS at 24 mo (n = 10)	Between-group difference, *P* value
Male sex, no. (%)	25 (60)	5 (50)	0.59
Mean age, yr (SD)	48.8 (9.5)	49.2 (12.4)	0.91
Time since last surgery, yr (SD)	4.6 (5.2)	5.2 (4.7)	0.74
>1 surgery, no. (%)	22 (52)	6 (60)	0.66
Employed, no. (%)	9 (21)	3 (30)	0.59
History of legal action related to FBSS, no. (%)	34 (81)	9 (90)	0.42
Unilateral leg pain, no. (%)	27 (64)	6 (60)	0.80
Bilateral leg pain, no. (%)	15 (36)	4 (40)	0.80
Back pain VAS, mean (SD)	55.0 (23.6)	52.7 (28.3)	0.80
Leg pain VAS, mean (SD)	77.6 (12.2)	69.3 (14.7)	0.07

[a] SCS, spinal cord stimulation; SD, standard deviation; FBSS, failed back surgery syndrome; VAS, visual analog scale.

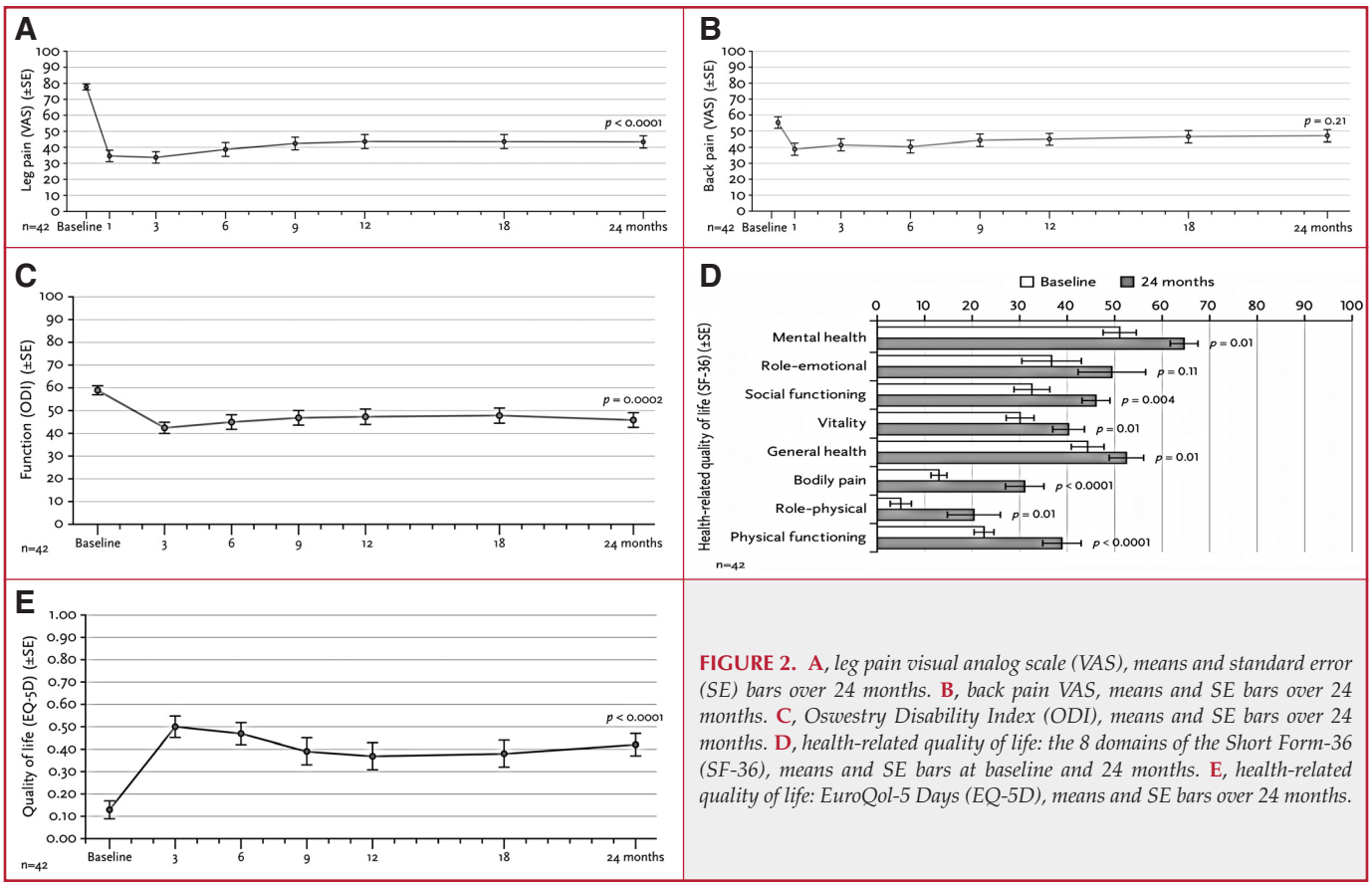

FIGURE 2. **A**, *leg pain visual analog scale (VAS), means and standard error (SE) bars over 24 months.* **B**, *back pain VAS, means and SE bars over 24 months.* **C**, *Oswestry Disability Index (ODI), means and SE bars over 24 months.* **D**, *health-related quality of life: the 8 domains of the Short Form-36 (SF-36), means and SE bars at baseline and 24 months.* **E**, *health-related quality of life: EuroQol-5 Days (EQ-5D), means and SE bars over 24 months.*

(37%) versus 1 CMM patient (2%) achieved the primary outcome ($P = 0.003$). In the most conservative scenario (i.e., assuming that patients who withdrew or were lost to follow-up in the SCS group were failures and their counterparts in the CMM group were successes), 17 (33%) of 52 patients randomized to SCS and 8 (17%) of 48 patients randomized to CMM achieved the primary outcome ($P = 0.07$). Of the 72 patients who received SCS as the final treatment, 34 (47%) achieved the primary outcome versus 1 (7%) of the 15 patients who received CMM as the final treatment ($P = 0.02$) (Fig. 4).

DISCUSSION

This long-term study shows that, in selected patients with FBSS, significant improvements in leg pain, functional capacity, and health-related quality of life recorded after 6 months of SCS treatment are sustained at 24 months (15). Furthermore, at 24 months, the addition of SCS to CMM continues to provide additional pain relief compared with CMM alone. This finding is consistent with the 3-year results of the single previously reported randomized controlled trial of SCS versus reoperation in FBSS patients (20).

Several investigators have called for long-term clinical trials of neurostimulation procedures for chronic neuropathic pain (4, 25). Although a few studies with follow-up of 10 years or more have been published (12, 13, 22, 27), the 2-year results reported here represent the longest randomized controlled trial-based report on so large a number of SCS patients. By comparison, pharmacological trials in neuropathic pain rarely report long-term outcomes; for example, a 2006 systematic review on the use of opioids in neuropathic pain identified 12 trials with a median follow-up of only 4.4 weeks (range, 1–6 weeks) (9).

The reported 31% of the 42 SCS patients experiencing device-related complications requiring surgical intervention falls within the previously reported range of 20 to 75% (3, 12, 16). In our study, the events recorded as complications were benign, reversible, and not incapacitating. Unlike the present study, many previous reports are single-center case series that often fail to report events that occur during the screening trial and might, therefore, underestimate "real-world" complication rates (24). Because SCS is a lifelong therapy, it is important, both clinically and economically, to note that the frequency of device-related revisions shows a marked reduction after the first year. Furthermore, 89% of our patients who experienced at least 1 device-related event stated that they would be willing to undergo the procedure again.

Although return to work can never be used as an outcome of an SCS trial because employment status is subject to many vari-

TABLE 2. Within-group comparison of outcomes[a]

	Baseline	1 mo	3 mo	6 mo	9 mo	12 mo	18 mo	24 mo	24 mo versus baseline *P* value[b]
Leg pain relief (%)[c]		n = 41	n = 42	n = 42	n = 41	n = 42	n = 42	n = 42	
≥30%		31 (76)	32 (76)	29 (69)	27 (66)	29 (69)	26 (62)	29 (69)	
≥50%		23 (56)	26 (62)	23 (55)	21 (51)	16 (38)	19 (45)	17 (40)	
≥80%		9 (22)	11 (26)	11 (26)	7 (17)	9 (21)	8 (19)	6 (14)	
Morphine, mg, mean (SE)									
Low[d]	81.4 (25.1)	65.8 (23.5)	69.4 (21.9)	81.8 (24.8)	85.7 (26.4)	85.6 (24.4)	81.1 (22.6)	83.2 (22.9)	0.94
High	93.2 (30.6)	73.8 (27.3)	80.3 (25.2)	94 (28)	100 (29.8)	97.1 (25.6)	94.3 (25.3)	99.3 (26.3)	0.86
Drug therapy (%)	n = 42	n = 42	n = 42	n = 42	n = 41	n = 42	n = 42	n = 42	
Opioids	30 (71)	24 (57)	24 (57)	25 (60)	25 (61)	25 (60)	25 (60)	26 (62)	0.34
NSAIDs	12 (29)	13 (31)	15 (36)	18 (43)	15 (37)	14 (33)	17 (40)	16 (38)	0.39
Antidepressants	13 (31)	12 (29)	13 (31)	12 (29)	13 (32)	13 (31)	14 (33)	14 (33)	1.00
Anticonvulsants	14 (33)	10 (24)	8 (19)	9 (21)	11 (27)	11 (26)	10 (24)	9 (21)	0.18
Nondrug therapy (%)	n = 42	n = 42	n = 42	n = 42	n = 41	n = 42	n = 42	n = 42	
Physical rehab	1 (2)	1 (2)	2 (5)	2 (5)	2 (5)	1 (2)	2 (5)	2 (5)	1.00
Psychological rehab	1 (2)	1 (2)	1 (2)	1 (2)	0	0	1 (2)	1(2)	1.00
Acupuncture	2 (5)	1 (2)	0	0	0	0	0	0	N/C
Massage	2 (3)	0	0	0	0	1 (2)	0	0	N/C
TENS	3 (7)	0	0	0	0	0	0	0	N/C
Patient satisfaction (%)[c]			n = 42	n = 42	n = 41	n = 42	n = 42	n = 42	
With pain relief			30 (71)	28 (67)	28 (70)	26 (62)	27 (64)	27 (66)	
With treatment			36 (86)	36 (88)	38 (93)	38 (93)	37 (88)	39 (93)	
Work status	n = 42	n = 42	n = 42	n = 42	n = 41	n = 42	n = 42	n = 42	
Working (%)[e]	9 (21)	5 (12)	10 (24)	12 (29)	11 (27)	11 (27)	12 (29)	11 (27)	

[a] SE, standard error; FBSS, failed back surgery syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; N/C, not calculable (division by zero); rehab, rehabilitation; TENS, transcutaneous electrical nerve stimulation.
[b] Adjusted for baseline value and age, sex, time since FBSS, number of spinal operations, and leg pain location.
[c] Adjusted for age, sex, time since FBSS, number of spinal operations, and leg pain location.
[d] Two different conversion ratios resulted in "low" and "high" equianalgesic doses of oral morphine.
[e] Of the 42 patients, 37 were of working age. Five patients were older than 65 years of age and did not work throughout the study.

ables beyond health status, including factors beyond a patient's control, workers who have been unemployed for 4 to 12 weeks as a result of back pain have a 10 to 40% risk of continued unemployment, and a year of absence renders return to work unlikely despite treatment outcome (29, 30). Thus, the fact that 11 (30%) of our 37 employment-age patients were working at 24 months is noteworthy, especially because 4 of the patients had been out of work for a mean of more than 2.5 years.

The PROCESS trial, from which our study subjects are drawn, had a number of strengths, including its 2-year follow-up period, pragmatic real-world design, few lost subjects, and careful and comprehensive collection of pain and patient-related outcomes. Study limitations include lack of patient, investigator, and assessor blinding and the high level of crossover after 6 months.

Without blinding, we cannot rule out a placebo effect, but blinding is a difficult issue with SCS because paraesthesia is elicited in the area of the pain. In addition, the implantation procedure might itself produce a placebo effect, but sham operations are ethically difficult to justify (28).

The high number of crossovers in the PROCESS trial compromised our ability to make an unbiased assessment of the relative effectiveness of SCS beyond 6 months. Compared with those who remained in their randomized group, the outcomes for crossovers might have been influenced by the therapy received initially and by a variable exposure time on the alternate therapy; therefore, we conducted the current analysis of patients randomized to SCS who were receiving stimulation at 24 months. We have an indication that this

TABLE 3. Spinal cord stimulation-related complications through 24 mo (n = 42)[a]

Event	No. of events	Patients with ≥1 event, no. (%)	Patients requiring surgical revision, no. (%)
Total	34	19 (45)	13 (31)
Hardware-related			
Electrode migration	9	6 (14)	6 (14)
Lead or extension fracture or torqued contacts	4	3 (7)	1 (2)
IPG migration	1	1 (2)	1 (2)
Total hardware-related	14	10 (26)	8 (19)
Technique			
Loss of therapeutic effect, lost or unpleasant paresthesia	5	5 (12)	2 (5)
Technique[b]	3	2 (5)	2 (5)
Biological			
Infection or wound breakdown	4	4 (10)	2 (5)
Pain at IPG incision site	5	5 (12)	1 (2)
IPG pocket fluid collection	3	2 (5)	0
Total biological	12	9 (21)	3 (7)

[a] IPG, implanted pulse generator.
[b] One suboptimal connection of extension to IPG led to intermittent stimulation, 1 anteriorly implanted electrode caused shocks, and 1 lead was cut during implant.

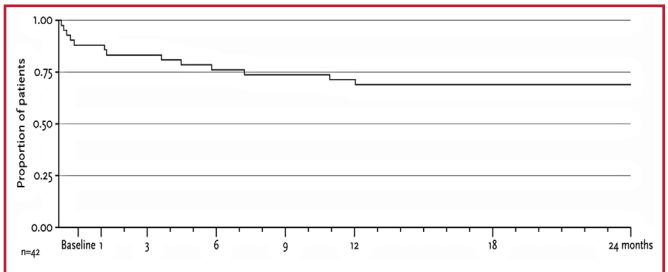

FIGURE 3. *Kaplan-Meier plot of time to first SCS-related complication requiring surgical revision.*

TABLE 4. Non-spinal cord stimulation-related adverse events through 24 months (n = 42)[a]

	No. of events	Patients with ≥1 event, no. (%)
Total	15	13 (31)
New illness, injury, or condition related to FBSS pain	8	7 (17)
Worsening of preexisting condition related to FBSS pain[b]	7	7 (17)

[a] FBSS, failed back surgery syndrome.
[b] One pump implanted after 12-month visit, 1 laminectomy after18-month visit, 1 patient on waiting list for fusion at study exit.

is not a highly selected subgroup, as its baseline characteristics are similar to those of the remaining 10 patients randomized to SCS.

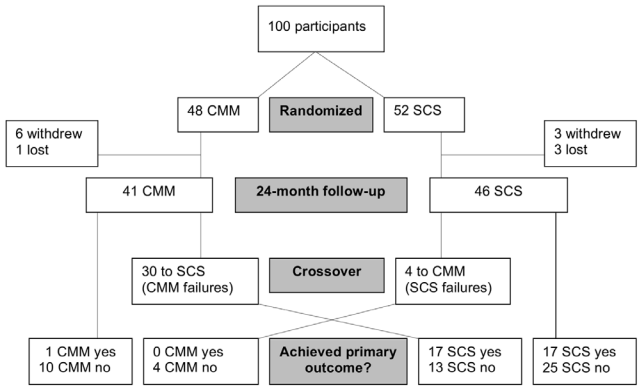

FIGURE 4. *Chart representing patient flow and the primary outcome at 2 years; 34 final treatment successes appear on the right (SCS side) and only 1 on the left (CMM side). In the "modified intention-to-treat" or "treated-as-intended" analysis (outcomes assigned to randomized group with crossover considered a failure), 17 SCS patients versus 1 CMM patient achieved the primary outcome of at least 50% leg pain relief. On the basis of the final treatment received, 34 of 72 patients achieved the primary outcome with SCS versus 1 of 15 patients with CMM.*

CONCLUSION

In selected patients with FBSS, treatment with SCS results in pain relief that is sustained at 24 months and is associated with patient satisfaction and clinically important improvements in functional capacity and health-related quality of life.

Disclosure

All logistical aspects of the study were managed and funded by Medtronic, Inc. The trial was designed and supervised by a Trial Steering Committee that consisted of 4 external advisors and 2 representatives from Medtronic, Inc. Data were collected and analyzed by Medtronic, Inc., under the direction of the committee. The manuscript was written by the independent members who had full, nonrestricted access to the data. EHC Hospital of Morges (Eric Buchser's employer), Rod S. Taylor, the Johns Hopkins University (Richard B. North's former employer), and the nonprofit Neuromodulation Foundation, Inc. (of which Richard B. North is a director), have received financial reimbursement as consultants for Medtronic, Inc.

REFERENCES

1. Barolat G, North RB: Spinal cord stimulation: Equipment and implantation techniques, in Burchiel K (ed): *Surgical Management of Pain*. New York, Thieme, 2002, pp 535–548.
2. Berger A, Dukes EM, Oster G: Clinical characteristics and economics costs of patients with painful neuropathic disorders. **J Pain** 5:143–149, 2004.
3. Cameron T: Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: A 20-year literature review. **J Neurosurg** 100:254–267, 2004.
4. Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, Simpson BA, Taylor RS: EFNS guidelines on neurostimulation therapy for neuropathic pain. **Eur J Neurol** 14:952–970, 2007.
5. Dworkin RH, Backonja N, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM: Advances in neuropathic pain: Diagnosis, mechanism and treatment recommendations. **Arch Neurol** 60:1524–1534, 2003.
6. European Medicines Agency Committee for Medicinal Products for Human Use: *Guideline on Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain*. http://www.emea.eu. Accessed March 19, 2008.
7. Fairbank J, Pynsent P: The Oswestry Disability Index. **Spine** 25:2940–2952, 2000.
8. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH: Algorithm for neuropathic pain treatment: An evidence based proposal. **Pain** 118:289–305, 2005.
9. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E: Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. **Can Med Assoc J** 174:1589–1594, 2006.
10. International Committee on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: *Statistical Principles for Clinical Trials: Guideline E9*, 1998, http://www.ich.org/LOB/media/MEDIA485.pdf. Accessed March 19, 2008.
11. Kind P: The EuroQoL instrument: An index of health-related quality of life, in Spilker B (ed): *Quality of Life and Pharmacoeconomics in Clinical Trials*. Philadelphia, Lippincott-Raven, 1996, pp 191–201.
12. Kumar K, Hunter G, Demeria D: Spinal cord stimulation in treatment of chronic benign pain: Challenges in treatment planning and present status, a 22-year experience. **Neurosurgery** 58:481–496, 2006.
13. Kumar K, Nath R, Wyant GM: Treatment of chronic pain by epidural spinal cord stimulation: A 10-year experience. **J Neurosurg** 75:402–407, 1991.
14. Kumar K, North RB, Taylor RS, Sculpher M, Van den Abeele C, Gehring M, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Fortini G, Richardson J, Buchser E, Tracey S, Reny P, Brookes M, Sabene S, Cano P, Banks C, Pengelly L, Adler R, Leruth S, Kelly C, Jacobs M: Spinal cord stimulation versus conventional medical management: A prospective, randomized, controlled, multicenter study of patients with failed back surgery syndrome (PROCESS study). **Neuromodulation** 8:213–218, 2005.
15. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB: Spinal cord stimulation versus conventional medical management for neuropathic pain: A multicentre randomised controlled trial in patients with failed back surgery syndrome. **Pain** 132:179–188, 2007.
16. Kumar K, Wilson JR, Taylor RS, Gupta S: Complications of spinal cord stimulation, suggestions to improve outcome, and financial impact. **J Neurosurg Spine** 5:191–203, 2006.
17. Manca A, Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, Taylor RJ, Goeree R, Sculpher MJ: Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial). **Eur J Pain** Epub March 20, 2008.
18. McHorney CA, Ware JE Jr, Raczek AE: The MOS 36-item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. **Med Care** 31:247–263, 1993.
19. Meyer-Rosberg K, Burckhardt CS, Huizar K, Kvarnström A, Nordfors LO, Kristofferson A: A comparison of the SF-36 and Nottingham Health Profile in patients with chronic neuropathic pain. **Eur J Pain** 5:391–403, 2001.
20. North RB, Kidd DH, Farrokhi F, Piantadosi S: Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: A randomized, controlled trial. **Neurosurgery** 56:98–107, 2005.
21. North RB, Kidd D, Shipley J, Taylor RS: Spinal cord stimulation versus reoperation for failed back surgery syndrome: A cost effectiveness and cost utility analysis based on a randomized, controlled trial. **Neurosurgery** 61:361–369, 2007.
22. North RB, Kidd DH, Zahurak M, James CS, Long DM: Spinal cord stimulation for chronic, intractable pain: Experience over two decades. **Neurosurgery** 32:384–395, 1993.
23. Sweetman SC (ed): *Martindale: The Complete Drug Reference*. London, Pharmaceutical Press, 2005, ed 34.
24. Taylor RS, Van Buyten JP, Buchser E: Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: A systematic review and analysis of prognostic factors. **Spine** 30:152–160, 2005.
25. Turner JA, Loeser JD, Deyo RA, Sanders SB: Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: A systematic review of effectiveness and complications. **Pain** 108:137–147, 2004.
26. Twycross R, Wilcock A, Charlesworth S, Dickman A (eds): *Radcliffe Palliative Care Formulary*. London, Medical Press, 2002, ed 2.
27. Van Buyten JP, Van Zundert J, Vueghs P, Vanduffel L: Efficacy of spinal cord stimulation: 10 years of experience in a pain centre in Belgium. **Eur J Pain** 5:299–307, 2001.
28. Van Zundert J: Clinical research in interventional pain management techniques: The clinician's point of view. **Pain Pract** 7:221–229, 2007.
29. Waddell G: The clinical course of low back pain, in *The Back Pain Revolution*. Edinburgh, Churchill Livingstone, 1998, ed 1, pp 103–107.
30. Waddell G, Burton AK: Occupational health guidelines for the management of low back pain at work: Evidence review. **Occup Med** 51:124–135, 2001.
31. Wilkinson HA: *The Failed Back Syndrome: Etiology and Therapy*. Philadelphia, Harper & Row, 1991, ed 2.

Acknowledgments

Study Coordinators: A. Smit, Pain Clinic, Morges Hospital, Morges, Switzerland; R. Adler, Pain Relief Unit, Rambam Medical Centre, Haifa, Israel; M. Brookes, Department of Pain and Anesthesia, James Cook University Hospital, Middlesbrough, England; A. Bacuzzi, M.D., Pain Clinic, Varese Regional Hospital and Macchi Foundation, Varese, Italy; P. Reny, Department of Neurosurgery, Montreal Neurological Institute and Hospital, Montreal, PQ, Canada; S. Tracey, Department of Neurosurgery, Regina General Hospital, Regina, SK, Canada; S. Sabene, Department of Functional Neurosurgery, Gemelli Catholic University Hospital, Rome, Italy; S. Leruth, Neurosurgery, Namur Regional Hospital, Namur, Belgium; J. Solivera, M.D., Department of Neurosurgery, Hospital Santa Creu I Sant Pau, Barcelona, Spain; L. Pengelly, Pain Clinic, Axxon Pain Medicine, Brisbane, Queensland, Australia; C. Kelly, Department of Pain and Anesthesia, Bradford Hospitals, Bradford, England; and C. Banks, Pain Clinic, Basildon and Thurrock University Hospitals, Basildon, Essex, England.

COMMENTS

This is an excellent article on a limited series of patients who received spinal cord stimulation (SCS) for neurogenic pain due to failed back

surgery syndrome (FBSS). We noted, with appreciation, the randomization of patients to be recruited and submitted alternatively to SCS and/or oral drug therapy. Moreover, this article is enriched by extensive statistical analysis of data on sufficient long-term follow-up examination of the patients.

The article is well written and the concepts are expressed clearly. These data support the concept that pain from FBSS seems to be one of the best indications for chronic SCS, and we obtained similar data in our experience with some 50 patients at long-term follow-up examinations ranging from 12 to 70 months.

The quantity of surgical complications is also similar and matches other case series reported so far but are not important in the overall clinical balance. Kumar et al. have provided an important contribution to the field of surgical management of pain that, in our opinion, will stand for a long time.

Ivano Dones
Giovanni Broggi
Milano, Italy

This is the best study of SCS for FBSS that has yet been performed. The quality of this work by Kumar et al. will certainly advance the field of SCS for FBSS. Interested readers should review the editorial published in *Pain* (2) that discussed the publication of the 6-month results of this study (1). The characteristics of this study include detailed patient flow analysis, randomization to the two treatment arms, power calculations to determine adequate sample sizes, standardized outcome measures that are in widespread use, assessment of both pain and quality of life at predetermined intervals for all patients, use of an intent to treat paradigm, listing of complications, and the "pragmatic" focus reflecting clinical practice. No study is perfect, and this one has some potentially worrisome factors. These include the fact that the patients in the control group received treatment that had already failed for them. In this sense, it is an enrichment study that will make the control group look worse. The fact that the study was funded by and actually performed by a device manufacturer and that many of the local investigators had links to the device manufacturer raises some questions about hidden biases. We do not know how typical the subjects were of patients referred to the investigators for SCS; that is, how generalizable are these results to the patients one sees in his or her practice? In addition, neither the patients, the physicians involved, nor the study evaluators were blinded to the patients' group assignment; of course, this blinding may not have been possible, but it still raises concerns.

It is useful to note that almost all of the complications occurred in the first year after implantation; this observation is important when one wishes to compare costs of various treatments. We remain in the dark, however, as to the specificity of the outcomes that are reported. Are they due to the effects of the electrical energy on the spinal cord? Are they due to nonspecific treatment effects such as the placebo response? How do these outcomes compare with an intensive rehabilitation program involving medication management, physical therapies, education, job training, and psychological treatments, i.e., multidisciplinary pain management?

Kumar et al. have presented a superb research project.

John D. Loeser
Seattle, Washington

1. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB: Spinal cord stimulation versus conventional medical management for neuropathic pain: A multicentre randomised controlled trial in patients with failed back surgery syndrome. **Pain** 132:179–188, 2007.
2. Turner JA, Deyo RA, Loeser JD: Spinal cord stimulation: stimulating questions. **Pain** 132:10–11, 2007.

The best way to view this study is to consider it as an open 24-month nonrandomized trial of SCS for patients with leg pain. The population was selected with strict entrance criteria and by a willingness to be randomized and followed for 2 years. The 14-center study only entered on average 2 patients per year. Of the 52 patients to receive surgery, 42 were followed for the 2 years and 37% of these patients had a 50% reduction of leg pain, the primary end point. The reduction in visual analog scale was prompt, but by 9 months was slightly less and did not change again. The use of oral narcotics remained the same, and the ability to work did not improve. However, a vast majority of patients were satisfied with the treatment despite the fact that 31% required reoperations.

Although the results of the study are clear, its implications are not. The title of the article seems to indicate that the 6-month randomized results favoring SCS are maintained over 2 years. Indeed the initial patients receiving SCS are about the same compared with themselves but not compared with the non-SCS group. The non-SCS group crossed over and became too small to compare. The desired randomized study could not be done in this patient group. Having patients remain as surgical controls for 2 years was obviously not considered a fair thing to do to them. To use the ethical language, there was not basic equipoise. The 2-year study was not a simple randomized controlled study but a delay to treatment study. This makes a difference because it limits what conclusions can be drawn. The SCS versus non-SCS illustrative analysis for 2 years in this article is inconclusive, misleading, and unnecessary. The fact that the patients receiving SCS stayed about the same for 2 years of treatment adequately shows that it was not just a transient 6-month effect.

Is this a good or bad result? It depends on who you are. Obviously the patients were happy in having some reduction in disabling pain even though the group as a whole had to endure a high revision rate and many adverse events. As one who has worked with and participated for more than 30 years in electrical stimulation for pain for FBSS, I can say that personally I am disappointed. No substantial improvement in results have occurred over all these years, all the devices currently made are about the same, and the studies show outcomes for leg pain that we already know from personal experience. We have landed short of our goal. The pain gate has not been closed with SCS; in fact, the gate theory of pain is now known to be incorrect. We need new ideas and a fresh start.

Richard D. Penn
Chicago, Illinois

SCS has been used for 40 years to treat chronic neuropathic pain. FBSS (also called postlaminectomy syndrome) is one of the most frequent indications for SCS, with numerous studies suggesting that SCS may be an effective treatment. This article by Kumar et al. and the Prospective Randomized Controlled Multicenter Trial of the Effectiveness of Spinal Cord Stimulation Study Group analyzes one subset of data from a large, multicenter, randomized trial of SCS for FBSS.

Patients were randomized to either SCS or conventional medical management, with the ability to cross over to the other treatment arm if the primary treatment failed. Kumar et al. described a "modified intention-to-treat" (or "treated as intended") analysis in which

outcomes are assigned on the basis of randomization group, with crossover considered to represent failure of a given treatment. This differs from standard intention-to-treat analysis, in which patients remain assigned to a treatment group regardless of final therapy. For example, using intention-to-treat analysis, a patient in whom conventional medical management failed and who crossed to SCS and then achieved a successful outcome would be considered a success of medical management, despite failure of the initial therapy and success of SCS.

Intention to treat provides the best estimate of efficacy when no patients are lost to follow-up, and few patients cross over to another treatment arm. The large number of crossovers in this study, as well as the loss of 13% of patients to follow-up, introduces unknown biases that prevent definitive conclusions from being drawn. However, Kumar et al. offer some data that strongly suggest that SCS is indeed superior to conventional medical management for the treatment of FBSS.

At 24 months, 42 of 46 available patients (from a total of 52 patients who were randomized to SCS) continued to use the therapy (>80%). More than 90% would repeat the operation for the same result. However, only 17 of 46 (37%) achieved the primary outcome measure of more than 50% relief of leg pain. If dropouts are conservatively considered as failures, the success rate declines to 33%. Patients reported statistically significant improvements in functional capacity (as assessed by the Oswestry Disability Index) and health-related quality of life (as assessed by the Short Form-36 and EuroQoL).

The complication rate of 45%, including the need for surgical revision in 31% of patients, falls within the range reported in the literature. This emphasizes the continued need for engineering of better and more robust systems and for improvements in surgical techniques to minimize the relatively high rate of therapy failure.

So is the glass half full or half empty regarding SCS for FBSS? Certainly conventional medical management provides little benefit by comparison. In an illustrative example, Kumar et al. pointed out that 47% of patients who received SCS as a final treatment were treatment successes versus only 7% of patients who received conventional medical management. In contrast, patients receiving SCS had high rates of satisfaction and significant improvements in quality of life. Despite the limitations of the Prospective Randomized Controlled Multicenter Trial of the Effectiveness of Spinal Cord Stimulation study, this report provides some of the best evidence to date supporting the efficacy of SCS for the treatment of FBSS.

Jaimie M. Henderson
Stanford, California

Surgical trials are extraordinarily difficult to perform, and Class I evidence is hard to obtain. The challenge is even greater when one is studying patients undergoing surgery for the treatment of pain. Many surgical trials have failed because of inadequate enrollment and subject dropout and crossover issues, all of which stem from subject bias and the lack of surgeon equipoise. With this background, Kumar et al. have been able to successfully conduct a prospective, randomized clinical trial comparing surgical treatment and conventional medical therapy for the treatment of an entity known as FBSS.

In this article, they reported on the 24-month outcomes of this important trial, demonstrating that the effect of SCS on pain relief (the primary outcome measure) is superior to that of conventional medical treatment 2 years after surgery. Other functional and quality-of-life measures were also captured in this study, demonstrating a superiority of outcomes in the SCS group compared with the group receiving conventional medical therapy.

Kumar et al. used an intention-to-treat analysis when comparing the outcomes of the two groups of patients to preserve the randomization of the study group assignment. However, recognizing the effect of treatment crossover into the SCS group, they also carried out an "as treated" analysis. This is an important secondary analysis, because crossover rates in surgery versus medical therapy studies may seriously compromise the comparison in the intention-to-treat analysis (1).

Kumar et al. have provided an important work. They have carried the freight for the rest of us and demonstrated that it is possible to conduct scientifically rigorous studies of surgical procedures even in patients with the most difficult conditions.

Oren Sagher
Ann Arbor, Michigan

1. Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Hanscom B, Skinner JS, Abdu WA, Hilibrand AS, Boden SD, Deyo RA: Surgical vs nonoperative treatment for lumbar disk herniation: The Spine Patient Outcomes Research Trial (SPORT): A randomized trial. **JAMA** 296:2441–2450, 2006.