Received: May 4, 2020 Revised: October 1, 2020 Accepted: October 2, 2020

(onlinelibrary.wiley.com) DOI: 10.1111/ner.13297

Higher Preimplantation Opioid Doses Associated With Long-Term Spinal Cord Stimulation Failure in 211 Patients With Failed Back Surgery Syndrome

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ABSTRACT

Objective: Spinal cord stimulation (SCS) is an effective treatment in failed back surgery syndrome (FBSS). We studied the effect of preimplantation opioid use on SCS outcome and the effect of SCS on opioid use during a two-year follow-up period.

Materials and methods: The study cohort included 211 consecutive FBSS patients who underwent an SCS trial from January 1997 to March 2014. Participants were divided into groups, which were as follows: 1) SCS trial only (n = 47), 2) successful SCS (implanted and in use throughout the two-year follow-up period, n = 131), and 3) unsuccessful SCS (implanted but later explanted or revised due to inadequate pain relief, n = 29). Patients who underwent explantation for other reasons (n = 4) were excluded. Opioid purchase data from January 1995 to March 2016 were retrieved from national registries.

Results: Higher preimplantation opioid doses associated with unsuccessful SCS (ROC: AUC = 0.66, p = 0.009), with 35 morphine milligram equivalents (MME)/day as the optimal cutoff value. All opioids were discontinued in 23% of patients with successful SCS, but in none of the patients with unsuccessful SCS (p = 0.004). Strong opioids were discontinued in 39% of patients with successful SCS, but in none of the patients with unsuccessful SCS (p = 0.04). Mean opioid dose escalated from 18 ± 4 MME/day to 36 ± 6 MME/day with successful SCS and from 22 ± 8 MME/day to 82 ± 21 MME/day with unsuccessful SCS (p < 0.001).

Conclusions: Higher preimplantation opioid doses were associated with SCS failure, suggesting the need for opioid tapering before implantation. With continuous SCS therapy and no explantation or revision due to inadequate pain relief, 39% of FBSS patients discontinued strong opioids, and 23% discontinued all opioids. This indicates that SCS should be considered before detrimental dose escalation.

Keywords: Failed back surgery syndrome, opioids, spinal cord stimulation

Conflict of Interest: All authors are affiliated with the Kuopio University Hospital or University of Eastern Finland. Dr Nissen has received funding from Finnish Association for the Study of Pain and travel funding from the Medtronic, Boston Scientific and Abbott St Jude Medical. Ms Ikäheimo, Dr Huttunen, Dr Jyrkkänen and Dr von und zu Fraunberg have received travel funding from the Medtronic and Abbott St Jude Medical. Dr Leinonen has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

INTRODUCTION

Opioid overuse is an increasing problem worldwide as evidenced by an increasing number of opioid-related overdose deaths (1,2). The risk of death in patients consuming over 80 mg/day of morphine milligram equivalents (MME) is sixfold, while in patients consuming over 120 MME/day, it is tenfold when compared with opioid-naïve patients (3–8). Concomitant use of benzodiazepines significantly elevates the risk of trauma, violence-related injuries, and overdose-related deaths (8,9). Opioid use is associated with cardiovascular diseases, motor vehicle accidents, and endocrinological dysfunction (10–12). In Finland, prevalence of opioid use increased from less than 1% to 7% from 1995 to 2016, which was explained by the change in the treatment of codeine-based opioids (13). Simultaneously, there was a 68%

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For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

Source(s) of financial support: University of Eastern Finland. This study is supported by Medtronic and State Research Funding of Kuopio University Hospital.

increase in doctors' prescriptions of strong opioids from 2012 to 2016 (14). Long-term opioid use may intensify and prolong neuropathic pain and may induce psychological impairment, especially in the case of strong opioids (15).

Failed back surgery syndrome (FBSS) is a difficult pain condition that lacks a curative treatment. For this reason, patients who respond poorly to other pain medications often start opioid treatment. According to current recommendations, these drugs should be used only as a third-line treatment, and the evidence supporting their use in treating neuropathic pain, such as FBSS, is only moderate (16–19). An alternative pain relief method for FBSS is spinal cord stimulation (SCS), which has proven to be a safe, cost-effective, and efficacious treatment in selected patients experiencing neuropathic pain (20,21). However, despite the side effects of opioids, they are often started before trialing SCS. Here, we have presented a retrospective analysis of opioid use among FBSS patients treated with SCS in a single institution during a 17-year period. Our objectives were to analyze 1) the prevalence of opioid use among SCS patients compared to a matched sample of the general population, 2) the effect of preimplantation opioid use on SCS outcome, and 3) the effect of SCS therapy on opioid use, including the discontinuation of strong opioids, during a two-year follow-up period.

MATERIALS AND METHODS

Study Population

Kuopio University Hospital (KUH) is a tertiary center that provides full-time acute and elective neurosurgical services for a catchment containing 850,000 people in Eastern and Central Finland. The study group consisted of all 211 patients who underwent an SCS trial for FBSS with a surgical paddle lead at KUH between January 1, 1997, and March 31, 2014. All patients were followed up for 24 months after the primary trial SCS implantation, and 147 were followed up for 60 months. A specialist pain physician, neurosurgeon, or orthopedic surgeon made the FBSS diagnosis. Patients had undergone at least one previous lumbar decompressive surgery due to disc herniation or spinal stenosis but suffered from radicular lower limb pain alone or combined with lumbar pain. Initial treatment, including oral analgesics and physical therapy, was provided according to current best practice. Patients with manifest psychiatric comorbidities were sent to psychiatric consultation. Untreated depression and other serious psychiatric illnesses were considered a contraindication for SCS. No structured opioid tapering scheme was yet available in the participating pain clinics during the study period.

Patients (n = 211) were divided into three groups, which were as follows 1) SCS trial only with no permanent implantation (n = 47), 2) successful SCS (SCS implanted and in use throughout the two-year follow-up period, n = 131), and 3) unsuccessful SCS (SCS implanted but later explanted or revised due to inadequate pain relief during the two-year follow-up period, n = 29). Patients who underwent explantation for reasons other than inadequate pain relief (n = 4) were excluded from the overall analysis (Fig. 1). All medical data from hospital records were reviewed for details regarding SCS treatment, complications, and revisions. Baseline characteristics included age, gender, duration and localization of pain, and previous lumbar surgeries and instrumented fusions. Patients' reported subjective pain relief at three months was collected retrospectively from patient records. The Institutional Review Board of Kuopio University Hospital approved the study protocol. Informed consent was not required by Finnish legislation, because the study was based on registry data, and patients were not contacted.

SCS Implantation

The SCS paddle-lead electrode (Resume 3586, Symmix 3982, Specify 2x4 3998, or Specify 5-6-5 39565, Medtronic, Minneapolis, MN, USA) was micro-surgically implanted into the epidural space under direct visual control with the operating microscope through hemilaminotomy under general anesthesia (22). The mean duration of the trial was 7.1 days (SD 2.1). After the trial period, patients who reported paresthesia that covered most of the limb pain area with adequate pain relief received an internal pulse generator (IPG; model 7425, model 37703, model 7427V, model 37702, or model 97702, Medtronic). All patients who received an IPG visited an outpatient clinic 2–4 months (mean 110 days) after surgery and later, as needed (total 394 visits).

Matched Controls

For each patient, we retrieved three individually matched controls from the Population Register Center of Finland. Controls (n = 663) were matched by age, sex, and birthplace. The index date for matching was the date of SCS implantation, and all controls were alive on this date. Of all controls, 627 were alive throughout the follow-up period and were included in the study.

Opioid Purchase Data

The Social Insurance Institution of Finland (SII) has maintained a nationwide registry of all patients granted fully refundable drugs since 1994, which includes opioids and medications for neuropathic pain. The SII is an independent social security institution under the supervision of the Finnish Parliament. The National Health Insurance (NHI) scheme is part of the Finnish social security system and is run by the SII. All permanent residents of Finland are covered under the NHI scheme. We retrieved data for all purchases of prescribed opioids between January 1, 1995, and March 31, 2016, including their purchase date, amount in defined daily doses (DDD), and anatomical therapeutic chemical (ATC) classification code. This allowed the quantification of opioid use for at least two years before and after SCS implantation for each patient. No patient was lost during the follow-up period. We examined opioid use during the five-year follow-up period for those eligible. Opioid purchase data was fused with medical record data using the unique personal identification codes of Finnish residents.

During the follow-up period, patients and controls used eight different opioids, which were as follows: morphine, methadone, tramadol, oxycodone, hydromorphone, fentanyl transdermal (TD), codeine with combinations, dextropropoxyphene, and buprenorphine TD. In Finland, these drugs are sold by prescription only. To calculate the MME of different opioids, we used the following classification according to the World Health Organization pain ladder and controlled substance schedules with conversion ratios suggested by the Centers for Disease Control and Prevention (CDC). Weak opioids included codeine (0.15), tramadol (0.10), buprenorphine TD (75), and dextropropoxyphene (0.2), and strong opioids included morphine (1.0), methadone (3.0), oxycodone (1.5), hydromorphone (4.0), and fentanyl TD (100) (4,23–25). The MME conversion factor for fentanyl patches was based on the assumption that one milligram of parenteral fentanyl is equivalent

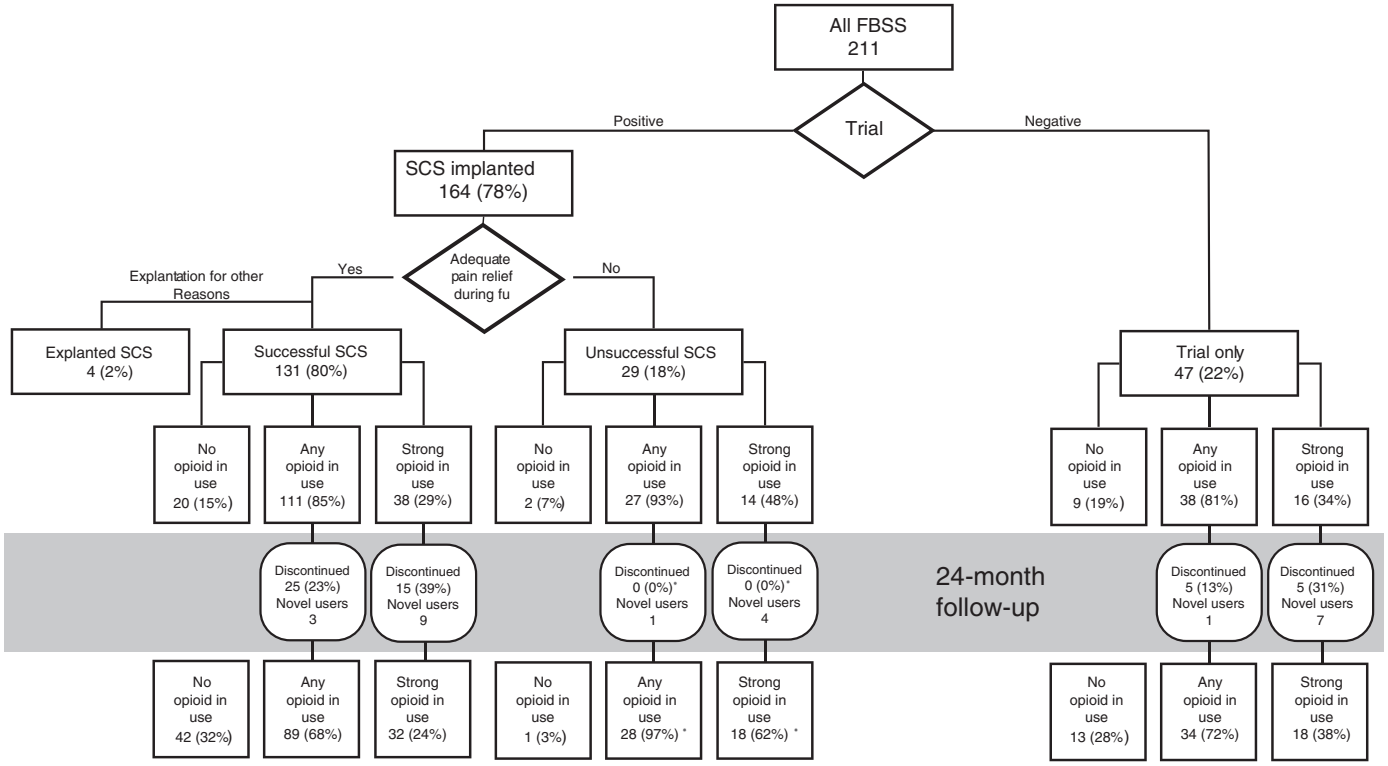

Figure 1. Flow chart of 211 consecutive SCS patients with FBSS treated at Kuopio University Hospital between January 1, 1997, and March 31, 2014, and their opioid use before and during the 24-months follow-up after SCS implantation. *Indicates a statistically significant difference ($p < 0.05$) compared to the successful SCS group in the Fisher's exact test.

to 100 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24-hour day, as it is used by the Centers for Medicare & Medicaid Services (CMS) (26). The MME conversion factor for methadone is used by the CMS when analyzing Medicare population opioid use (27).

Opioid discontinuation was defined as one or more purchases during the 18 months before the SCS trial or implantation but no purchases during the follow-up period of 18 months starting after a 6-month washout period. Medication data were acquired with the permission of the Social Insurance Institution of Finland, and matched controls were retrieved with the permission of the Population Registry of Finland. These data were merged with medical records with the permission of the Ministry of Social Affairs and Health of Finland.

Determination of Morphine Milligram Equivalent Threshold for SCS Failure

In this study, ROC analysis was used to evaluate the accuracy and optimal cutoff value for participants' preimplantation opioid dose (MME/day), which was used to classify patients into successful or unsuccessful SCS groups and was calculated as mean daily opioid use during the six months preceding SCS implantation. The optimal cutoff value was defined as MME/day, which maximized the sum of specificity and sensitivity (Youden index) (28).

Statistical Analysis

Categorical data have been presented as frequencies and proportions and assessed with chi-square or Fisher's exact tests as appropriate. Normality was assessed using the Shapiro–Wilk test. Continuous data that was not normally distributed was assessed with the Mann–Whitney *U*-test. Binary logistic regression analysis was used to compare SCS patient groups with controls, with age and gender as covariates. All SCS patients were used as the reference compared with controls, and the successful SCS group was used as the reference compared with other groups. A linear mixed effect model was used to determine interactions with the following covariates: time (categorical), group, and time * group, with opioid use as the dependent variable. All two-sided *p*-values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics and Opioid Use in 211 SCS Patients

Based on a 1-week trial, a SCS device was implanted in 164 of 211 (78%) patients. Of these, 138 (78%) were opioid users, and 52 (33%) were using strong opioids. The remaining 47 patients did not experience adequate pain relief and had their electrodes removed. Of these, 38 (81%) were opioid users ($p = 0.36$ compared to patients who received a permanent SCS device after trial), and 16 (34%) were using strong opioids ($p = 0.86$; Fig. 1). During the two-year period after implantation, the successful SCS group, comprising 131 patients, continued to use SCS and did not require explantation or revision due to inadequate pain relief. Information on pain relief was missing from six patients in this group, leaving 125 with complete sets of data. Of these 125 patients with successful SCS, 100 (80%) reported adequate pain relief at three months. There were 29 patients in the unsuccessful SCS group, comprising 19 (12%) who underwent permanent explantation of their SCS devices and 10 (6%) who

underwent revision due to inadequate pain relief. Of these 29 patients, one had missing information on pain relief, and seven (25%) reported adequate pain relief at three months ($p < 0.01$, compared with successful SCS). Overall, four patients had their SCS devices explanted for reasons other than inadequate pain relief. Of these, one had a hematoma, one had IPG discomfort, one experienced electrode migration, and one did not need SCS anymore. These patients were excluded from further analyses (Fig. 1).

Oxycodone and transdermal fentanyl were the most commonly used strong opioids, with median doses of 21.7 and 37.1 MME/day, respectively. The most commonly used weak opioids were tramadol and combined codeine/paracetamol, with median doses of 9.7 and 1.7 MME/day, respectively (Table 1). Strong opioid use was more common in patients with combined leg and back pain (44 of 118 patients, 37%) than in patients with isolated limb pain (24 of 89 patients, 27%; $p = 0.078$), although the difference was not statistically significant. Strong opioid use was more frequent in patients with permanent or explanted instrumented spinal fusion (30 of 67 patients, 45%) than in patients without instrumentation (38 of 140 patients, 27%; $p = 0.017$; Table 2).

Opioid Use During the Follow-Up Period After SCS Implantation

We studied opioid use in 207 patients who underwent SCS trial or implantation during an 18-month follow-up period, which started 6 months after the SCS trial or implantation (Fig. 1). Opioid use was significantly less frequent in patients with successful (68%) than unsuccessful (97%) SCS ($p = 0.001$), and strong opioid use was significantly less frequent in patients with successful (24%) than unsuccessful (62%) SCS ($p < 0.001$). Patients who underwent successful SCS seemed to use strong opioids less frequently (24%) than patients in the SCS trial (38%), although the difference was not statistically significant ($p = 0.054$; Fig. 1). Opioid dose escalated in all SCS groups during the follow-up period but did not escalate in controls (Table 3, Fig. 2). In the unsuccessful SCS group, mean opioid dose increased from 22 ± 8 MME/day (mean ± SEM) to 82 ± 21 MME/day, whereas in the successful SCS group, the dose increased from 18 ± 4 to 36 ± 6 MME/day. Dose escalation was more prominent in strong than weak opioids (Fig. 2; fixed effect model with all opioids: time $p < 0.001$, SCS group $p = 0.05$, and time * SCS group $p < 0.001$; strong opioids: time $p < 0.001$, SCS group $p = 0.04$, and time * SCS group $p < 0.001$; weak opioids: time $p = 0.16$, SCS group $p = 0.11$, and time * SCS group $p = 0.29$). Opioid use was stable in controls, at 0.4 MME/day, throughout the follow-up period.

Opioid Use Associates With Unsuccessful SCS

Higher preimplantation opioid doses associated with unsuccessful SCS in a bivariate logistic regression with opioid dose as a continuous variable adjusted for age and gender (odds ratio [OR] = 1.01, 95% confidence interval [CI] 1.00–1.01, $p = 0.037$; Table 3). Moreover, patients with unsuccessful SCS had a more rapid increase of opioid therapy in the 24 months before implant (from 21.5 to 50.5 MME/day) than patients with successful SCS (from 17.5 to 30.2 MME/day) (Fig. 2; fixed effect model with all opioids: time * SCS group $p = 0.026$). In addition, ROC analysis with AUC 0.66 ($p = 0.009$) yielded the optimal cutoff value of 35 MME/day (mean opioid use during last six months before implantation) show a risk for unsuccessful SCS (Fig. 3). Based on ROC analysis, we categorized opioid users into two groups ≤35 and >35 MME/day and performed bivariate logistic regression with age and gender as covariates. In this analysis, an opioid dose

Table 1. The Most Commonly Used Opioids and Their Usage Before and After SCS.

		Successful SCS		Unsuccessful SCS			Trial only		
		n	%	*n*	%	*p*	*n*	%	*p*
Oxycodone									
	Use before SCS (*n*, %)	30	23	11	38	0.094	15	32	0.224
	Use continued after SCS (*n*, %)	20	15	11	38	0.005	9	19	0.538
	Use discontinued after SCS (*n*, %)	10	8	0	0	0.126	6	13	0.293
	Use started after SCS (*n*, %)	8	6	6	21	0.012	4	9	0.574
Fentanyl									
	Use before SCS (*n*, %)	9	7	3	10	0.551	5	11	0.412
	Use continued after SCS (*n*, %)	1	1	3	10	0.003	2	4	0.112
	Use discontinued after SCS (*n*, %)	8	6	0	0	0.173	3	6	0.946
	Use started after SCS (*n*, %)	5	4	3	10	0.146	7	15	0.010
Tramadol									
	Use before SCS (*n*, %)	74	57	15	52	0.641	27	57	0.910
	Use continued after SCS (*n*, %)	41	31	9	31	0.978	18	38	0.383
	Use discontinued after SCS (*n*, %)	33	25	6	21	0.611	9	19	0.404
	Use started after SCS (*n*, %)	6	5	2	7	0.606	1	2	0.459
Codeine									
	Use before SCS (*n*, %)	21	16	9	31	0.062	6	13	0.594
	Use continued after SCS (*n*, %)	12	9	6	21	0.076	1	2	0.113
	Use discontinued after SCS (*n*, %)	9	7	1	10	0.522	5	11	0.412
	Use started after SCS (*n*, %)	2	2	1	3	0.491	2	3	0.280

Note: The p-Value is calculated using fisher's exact test and compared to the successful SCS group. Successful SCS = SCS implanted and in use throughout the two-year follow-up; Unsuccessful SCS = SCS implanted, but later explanted or revised due to inadequate pain relief during the two-year follow-up; Trial only = SCS trial only with no permanent implantation.

Table 2. Demographics and Clinical Characteristics of 207 Patients With SCS for FBSS and the Associated SCS Outcome and Opioid Use.

	All FBSS patients (n = 207)			Successful SCS (n = 131)			Unsuccessful SCS (n = 29)			Trial only (n = 47)		
	No opioid (n = 31)	Only weak opioid (n = 108)	Strong opioid (n = 68)	No opioid (n = 20)	Only weak opioid (n = 73)	Strong opioid (n = 38)	No opioid (n = 2)	Only weak opioid (n = 13)	Strong opioid (n = 14)	No opioid (n = 9)	Only weak opioid (n = 22)	Strong opioid (n = 16)
Gender												
Female	13 (42%)	56 (52%)	31 (46%)	8 (40%)	39 (53%)	18 (47%)	0 (0%)	6 (46%)	8 (57%)	5 (56%)	11 (50%)	5 (31%)
Male	18 (58%)	52 (48%)	37 (54%)	12 (60%)	34 (47%)	20 (53%)	2 (100%)	7 (54%)	6 (43%)	4 (44%)	11 (50%)	11 (69%)
Age (mean ± SD)	51 (10)	48 (11)	47 (10)	49 (11)	48 (10)	47 (9.4)	54 (7.8)	62 (5.7)	49 (16)	47 (13)	54 (7.8)	47 (12)
Location of pain												
Leg	18 (58%)	47 (44%)	24 (35%)	12 (60%)	33 (45%)	14 (37%)	1 (50%)	6 (46%)	3 (21%)	5 (56%)	8 (36%)	7 (44%)
Leg and back	13 (42%)	61 (57%)	44 (65%)	8 (40%)	40 (55%)	24 (63%)	1 (50%)	7 (54%)	11 (79%)	4 (44%)	14 (64%)	9 (56%)
Duration of pain in years (mean ± SD)	6.1 (5.5)	7.7 (6.8)	7.7 (6.8)	5.6 (4.7)	7.8 (6.7)	6.7 (5.4)	7.1 (7.8)	6.5 (0.7)	5.8 (4.4)	8.3 (7.9)	7.1 (7.8)	8.6 (7.5)
Level of operation												
L4–L5 and above	16 (52%)	40 (37%)	27 (40%)	11 (55%)	25 (34%)	16 (42%)	1 (50%)	5 (39%)	4 (29%)	4 (44%)	10 (46%)	7 (44%)
L5–S1	6 (19%)	35 (32%)	20 (29%)	3 (15%)	28 (38%)	12 (32%)	0 (0%)	5 (39%)	4 (29%)	3 (33%)	2 (9%)	4 (25%)
Multiple levels	9 (29%)	33 (31%)	21 (31%)	6 (30%)	20 (27%)	10 (26%)	1 (50%)	3 (23%)	6 (43%)	2 (22%)	10 (46%)	5 (31%)
Reason for operation												
Disc herniation	16 (52%)	53 (49%)	39 (57%)	10 (50%)	37 (51%)	25 (66%)	1 (50%)	5 (39%)	6 (43%)	5 (56%)	11 (50%)	8 (50%)
Stenosis	6 (19%)	28 (26%)	17 (25%)	7 (35%)	17 (23%)	7 (18%)	0 (0%)	4 (31%)	7 (50%)	1 (11%)	7 (32%)	3 (19%)
Both	9 (29%)	27 (25%)	12 (18%)	3 (15%)	19 (26%)	6 (16%)	1 (50%)	4 (31%)	1 (7%)	3 (33%)	4 (18%)	5 (31%)
Number of previous operations (mean ± SD)	2.1 (1.6)	2.3 (1.4)	2.5 (1.8)	2.3 (1.8)	2.2 (1.3)	2.3 (1.4)	2.0 (1.1)	1.5 (0.7)	3.1 (2.1)	2.7 (2.5)	2.0 (1.1)	2.2 (0.7)
Spinal fusion												
No	25 (81%)	77 (71%)	38 (56%)	16 (80%)	53 (73%)	21 (55%)	2 (100%)	8 (62%)	7 (50%)	7 (78%)	16 (73%)	10 (63%)
Yes or removed	6 (19%)	31 (29%)	30 (44%)	4 (20%)	20 (27%)	17 (45%)	0 (0%)	5 (39%)	7 (50%)	2 (22%)	6 (27%)	6 (38%)
Electrode location												
T9–T10	22 (71%)	62 (57%)	50 (74%)	14 (70%)	41 (56%)	31 (82%)	2 (100%)	7 (54%)	8 (57%)	6 (67%)	14 (64%)	11 (69%)
Other	9 (29%)	46 (43%)	18 (27%)	6 (30%)	32 (44%)	7 (18%)	0 (0%)	6 (46%)	6 (43%)	3 (33%)	8 (36%)	5 (31%)
Type of electrode												
Symmix/resume 1 × 4	28 (90%)	95 (88%)	56 (82%)	17 (85%)	67 (92%)	31 (82%)	2 (100%)	8 (62%)	11 (79%)	9 (100%)	20 (91%)	14 (88%)
Specify 5 – 6 – 5/2 × 4	3 (10%)	13 (12%)	12 (18%)	3 (15%)	6 (8%)	7 (18%)	0 (0%)	5 (39%)	3 (21%)	0 (0%)	2 (9%)	2 (13%)

Successful SCS = SCS implanted and in use throughout the two-year follow-up; Unsuccessful SCS = SCS implanted, but later explanted or revised due to inadequate pain relief during the two-year follow-up; Trial only = SCS trial only with no permanent implantation.

Table 3. Opioid Usage and Doses Before and After Implantation of SCS for FBSS in Association With SCS Outcome.

	Successful SCS	Unsuccessful SCS	OR (95% CI) ref = successful SCS	*p*	Trial only	OR (95% CI) ref = successful SCS	*p*
Opioid dose before implantation (mean mg MME/day ±SEM)	30.2 (4.4)	56.5 (14.6)	1.01 (1.00–1.01)	0.037	40.2 (10.8)	1.00 (1.00–1.01)	0.31
Opioid use over 35 MME/day before implantation	28 (21%)	15 (52%)	4.31 (1.82–10.2)	0.001	14 (30%)	1.54 (0.72–3.28)	0.26
Opioid use after implantation				<0.001			0.23
No use	42 (32%)	1 (3%)	1		13 (28%)	1	
Only weak opioid in use	70 (53%)	20 (69%)	10 (1.1–92)	0.041	25 (53%)	0.87 (0.36–2.1)	0.75
Strong opioid in use	32 (24%)	18 (62%)	51 (5–480)	0.001	18 (38%)	1.8 (0.71–4.5)	0.21
Opioid dose after implantation (mean mg MME/day ±SEM)	36.1 (6.1)	81.7 (20.9)	1.01 (1.00–1.01)	0.013	49.7 (10.8)	1.00 (1.00–1.01)	0.28

Note: Opioid doses are calculated as mean daily use during six months before implantation and 18 to 24 months after implantation. p-Values are calculated using bivariate logistic regression, with age and gender as covariates and the successful SCS group as a reference. Successful SCS = SCS implanted and in use throughout the two-year follow-up; Unsuccessful SCS = SCS implanted, but later explanted or revised due to inadequate pain relief during the two-year follow-up; Trial only = SCS trial only with no permanent implantation.

of >35 MME/day associated with unsuccessful SCS (OR = 4.3, 95% CI 1.8–10, $p = 0.001$; Table 3).

Opioid Discontinuation After Successful SCS Treatment

Of all included 207 patients, 176 were using opioids before their SCS trial (111 with successful SCS, 27 with unsuccessful SCS, and 38 with only an SCS trial; Fig. 1). In those with successful SCS, 25 of 111 (23%) discontinued all opioids compared to none of the 27 patients with unsuccessful SCS ($p = 0.004$) and five of the 38 (13%) patients who underwent only the SCS trial ($p = 0.25$). Strong opioids were discontinued in 15 of 38 (39%) patients with successful SCS compared to none of the 14 patients with unsuccessful SCS ($p = 0.04$) and five of 16 (31%) patients who undertook only the SCS trial ($p = 0.76$).

Novel Use After SCS Implantation During the Follow-Up Period After SCS Implantation

In total, 9 of the 93 (10%) patients with successful SCS who had not purchased strong opioids prior to their SCS implantation started strong opioid use during the follow-up period. These patients were defined as novel users. Of these, four had a revision or underwent explantation after the follow-up period (mean 46 months, SD 16 months). In addition, three patients had indications for opioid use other than worsened neuropathic leg pain, including one patient with cancer, one with new back pain without leg pain, and one with bone necrosis. In two patients, the reason for new opioid use was a worsening of their leg pain.

Opioid Purchases by SCS Patients Compared to 627 Matched Controls

During the period starting 24 months before and ending 24 months after SCS trial or implantation, 184 (87%) of 211 SCS patients made at least one opioid purchase compared with 41 (7%) of their 627 matched controls ($p < 0.001$). Strong opioids were purchased by 90 (42%) of the patients and three (1%) of their matched controls ($p < 0.001$). The total number of opioid purchases for 211 SCS patients was 5376, costing 380,883 euros. During the same period, their 627 matched controls made 441 purchases at a cost of 25,168 euros (data not shown).

Opioid Dose Five Years After SCS Trial or Implantation in 147 Patients and Their 441 Matched Controls

A five-year follow-up was accomplished for 147 SCS patients, during which 85 patients (58%) had SCS implanted and in place throughout the period, and 25 patients (17%) had SCS explanted or revised due to inadequate pain relief. Of all patients followed up at five years, 37 patients (25%) had undergone only an SCS trial. Mean opioid doses in these patients five years after the SCS trial or implantation were 42 ± 11 MME/day (mean ± SEM), 103 ± 31 MME/day ($p = 0.002$), and 84 ± 26 MME/day ($p = 0.06$), respectively. In contrast, their matched controls used opioids 0.1 ± 0.05 MME/day ($p < 0.001$) five years after the index date without dose escalation (Fig. 4).

DISCUSSION

We conducted a study of 211 consecutive FBSS patients trialed for SCS in a single tertiary center. Of them, 131 patients were able to continue SCS therapy throughout the two-year follow-up with no explantation or revision due to inadequate pain relief. Of the opioid users among them, 39% discontinued strong opioids and 23% discontinued all opioids. This implied that successful SCS therapy delivered as part of multidisciplinary pain care may assist in opioid tapering. This is in line with previous studies. In SENZA-RCT 36% of patients with high-frequency stimulation decreased or discontinued opioid use in contrast to 26% of patients with traditional stimulation. In the study of Falowski et al., 19% of patients with Burst SCS therapy discontinued opioid use. In a large registry-based study of over 5000 SCS patients, 47% of patients had an MME decrease after SCS implant (29–32). Our study was the first to use national registry data collected on a daily basis with no dropouts. This strategy is much more reliable than using retrospective self-reported use. Illegal use is not included in the registries; however, opioid abuse is uncommon in Finland, with only 2% of the Finnish population reporting nonmedical use of opioids (33). Data for all purchased opioids have been included in this study. It is possible, though unlikely, that purchased opioids were not consumed by the patients themselves.

Patients with high-dose opioid use were at higher risk of failing the SCS therapy. According to the CDC guidelines, clinicians

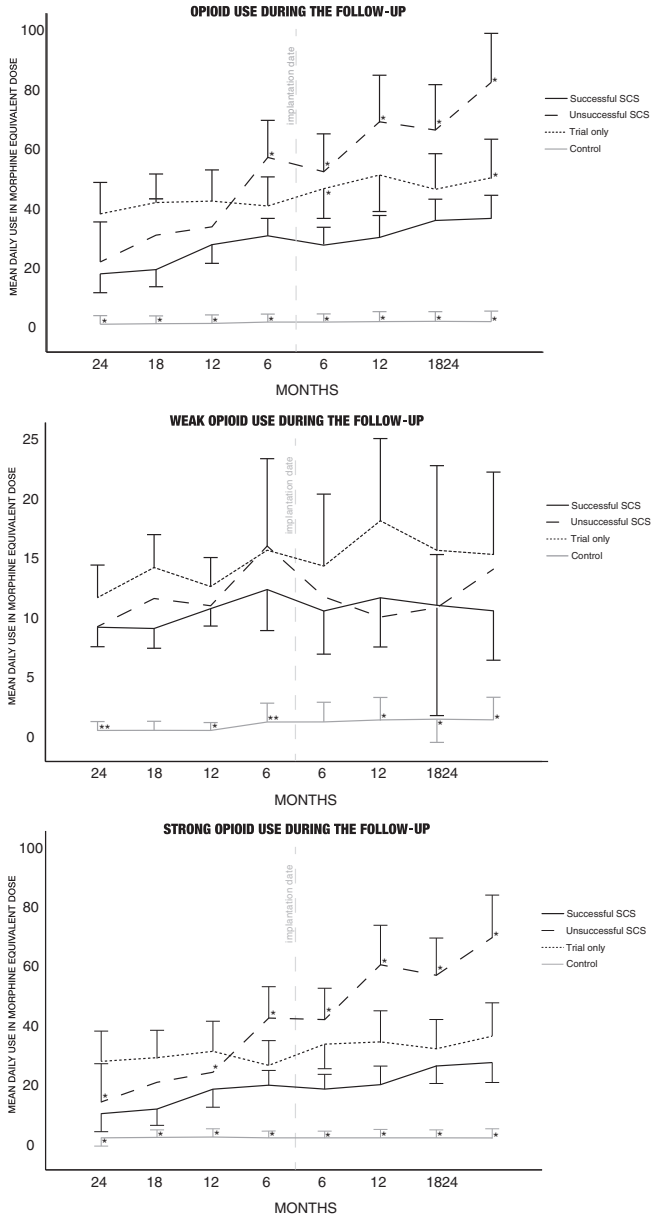

Figure 2. Mean daily opioid use 24 months before and after implantation of SCS in 207 FBSS patients at Kuopio University Hospital and their 627 matched controls. Trial only = SCS trial only with no permanent implantation, $n = 47$; Successful SCS = SCS implanted and in use throughout the two-year follow-up period, $n = 131$; Unsuccessful SCS = SCS implanted but later explanted or revised due to inadequate pain relief during the two-year follow-up period, $n = 29$. Mean daily dose in morphine equivalent milligrams was calculated as the average total purchased opioids during a specific six-month period (0–6, 6–12, 12–18, and 18–24 months before and after SCS). *Indicates a statistically significant difference ($p < 0.05$) compared to the successful SCS group in the Mann–Whitney *U*-test.

should carefully reassess the evidence of individual benefits and risks when increasing a patient's dosage to 50 MME/day and should avoid increasing a patient's dosage to 90 MME/day (4). Our recommendation is that SCS should be considered in suitable cases before starting long-term opioid use. Of patients with no opioid in use during the last six months before SCS implantation, only 8% had a later SCS failure, in contrast to 23% of opioid users. If opioids cannot be discontinued, then they should be stabilized or individually tapered to optimize the effect of SCS treatment. In contrast to previous studies (29,34), patients who underwent successful SCS treatment and continued using opioids increased their average opioid dose. However, dose escalation was steeper in patients with unsuccessful SCS treatment. This indicated that close contact with pain clinics should be advocated after SCS implantation to enable opioid tapering for all patients. This is even more important for patients who have undergone unsuccessful SCS, because they are at greater risk of opioid dose escalation.

Patients with the most severe leg and back pain or instrumented fusion required higher doses of opioids. It could be hypothesized that these patients failed SCS due to the inability of the therapy to treat severe FBSS. There is contradictory evidence of effect of pain level on SCS outcome; higher pain scores have predicted either better SCS outcome (35), or need for later SCS revision (36).

Patients with unsuccessful SCS had a more rapid increase of opioid therapy during two years before implant than patients with successful SCS. The rapid increase in opioid dosage and SCS loss of efficacy can have many causes, varying from the kind of pain to psycho-social problems. The supposed relationship between opioid tolerance and SCS loss of efficacy may indicate that patients develop a similar tolerance to SCS treatment. We conclude that higher preimplantation opioid dose rather than pain level is the risk factor for late SCS failure.

During the five-year follow-up, 20 SCS devices were explanted and 5 were revised due to inadequate pain relief. The explantation rates were 9% during the first year, 3% during the second year, and lower in later years. This is in line with a previous study of van Buyten et al. reporting annual explantation rate of 8% during a median follow-up of 2.2 years (37). In a recent study, Dougherty et al. reported a lower 10% explantation rate due to non-infectious reasons in five-year follow-up (38). Patients with unsuccessful long-term implants are in high risk of psychiatric and other comorbidities (39). This study shows that they are also in the highest risk of problematic opioid use and need active multidisciplinary surveillance and rehabilitation.

The unsuccessful SCS group included 10 patients with electrode revisions due to inadequate pain relief. Although they continued to use SCS throughout the study period, their opioid dose escalated more than the average, indicating a probable lack of SCS treatment effect. According to our previous study, over 30% of patients with revisions carried out due to inadequate pain relief later had their SCS device explanted (33).

Patients who underwent only the SCS trial used less opioids throughout the two-year follow-up period than patients with unsuccessful long-term SCS implants. However, these differences were not statistically significant at any time point (data not shown). In previous studies on similar populations, patients who failed in the trial phase were more often in a disability pension (40) and had a longer pain history (41). There may be other yet unknown psychological factors, which influence the decision to start lifelong SCS therapy.

This was a retrospective study with obvious limitations. Reliable information about pain relief or changes in quality of life related to SCS or opioid use is lacking, because no structured questionnaires or psychological evaluations were administered. We defined successful SCS as occurring in patients who did not undergo explantation or revision due to inadequate pain relief within the study period. This hard endpoint has been used in several earlier registry-based studies (30,37). There may be patients

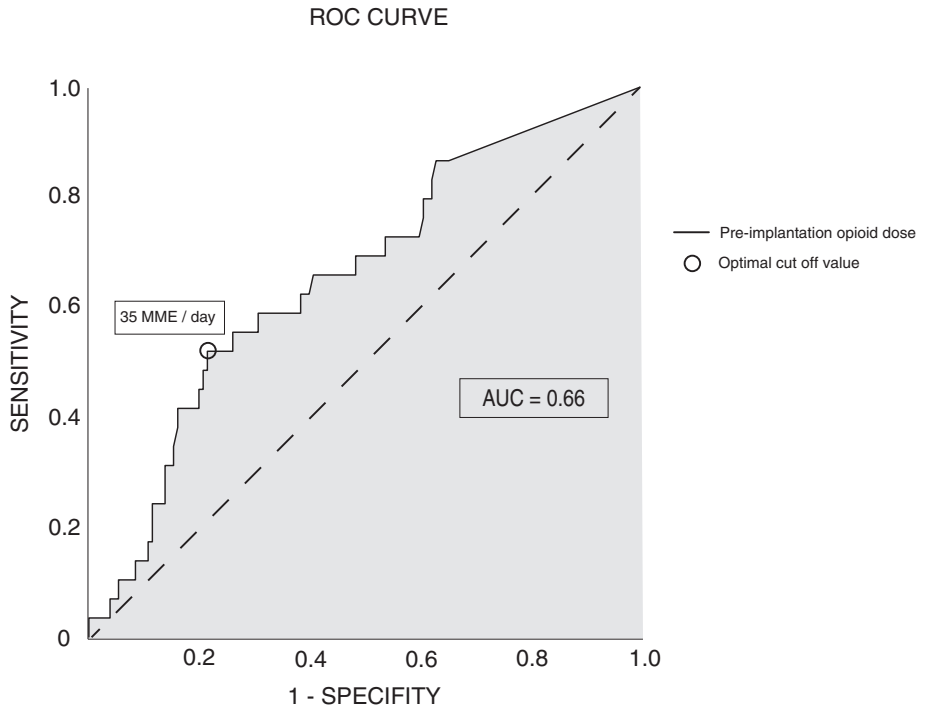

Figure 3. ROC curve determining accuracy and the optimal cutoff value for the preimplantation opioid use to classify patients into successful SCS or unsuccessful SCS group. Opioid doses were calculated as mean daily morphine milligram equivalents (MME) during six months before implantation. Successful SCS = SCS implanted and in use throughout the two-year follow-up, $n = 131$; Unsuccessful SCS = SCS implanted, but later explanted or revised due to inadequate pain relief during the two-year follow-up, $n = 29$. Optimal cutoff value was defined as MME/day that maximized the sum of specificity and sensitivity, i.e., Youden index. AUC, area under curve.

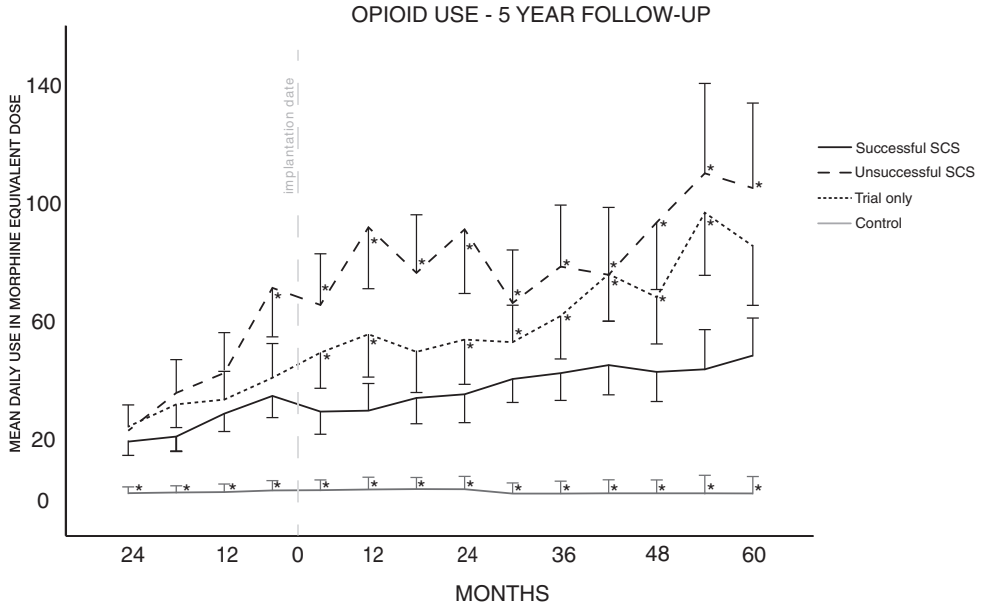

Figure 4. Mean daily opioid use during a five-year follow-up in 147 SCS patients with FBSS and their 441 matched controls. Trial only = SCS trial only with no permanent implantation, $n = 37$; Successful SCS = SCS implanted and in use throughout the five-year follow-up period, $n = 85$; Unsuccessful SCS = SCS implanted but later explanted or revised due to inadequate pain relief during the five-year follow-up period, $n = 25$. *Indicates a statistically significant difference ($p < 0.05$) compared to the successful SCS group in the Mann–Whitney *U*-test.

who have not benefited from SCS therapy despite continuous and uneventful use throughout the follow-up. Our previous study of this cohort showed that majority of patients with continuous SCS were satisfied with the therapy (41).

In this study, all implantations were performed using a surgical paddle lead, which may have caused scarring and suboptimal placement. Patients with surgical paddle lead placement are also at a higher risk of increased post-procedural pain. Hence, we have

included a six months wash-out period after operation before analyzing opioid use.

During the study period of nearly 20 years, the neurosurgeons performing implantations have changed, as have the criteria for permanent SCS implantation. In addition, SCS devices have evolved. All patients in this study had surgical paddle leads with tonic wave forms, although the current trend is towards percutaneous leads and different wave-modalities, such as burst, high-frequency, or closed loop stimulation. This study shows that even traditional tonic stimulation may allow opioid dose reduction or even discontinuation in selected patients. In SENZA-RCT, high-frequency stimulation yielded higher percentage of opioid dose reduction or discontinuation than traditional stimulation, indicating that novel wave-modalities may provide additional benefit (31). Substantial differences may also exist in the practices of opioid prescription between pain centers and clinicians, but this information cannot be retrieved from the data.

CONCLUSIONS

Higher preimplantation opioid doses were associated with SCS failure, suggesting that opioids should be tapered before implantation whenever possible. With continuous SCS therapy with no explantation or revision due to inadequate pain relief, 23% of FBSS patients discontinued all opioids, and 38% discontinued strong opioids. This indicates that SCS should be considered before detrimental opioid dose escalation.

Authorship Statements

Dr. Nissen was the main author of the manuscript and made the main part of statistical analysis and data preparation. Ms. Ikäheimo participated in the data collection and designing the study. Drs. Jyrkkänen and Huttunen provided statistical support in analyzing the data and drafting the manuscript. Professor Leinonen helped in designing the study and drafting the manuscript. Dr. von und zu Fraunberg was the main supervisor of the study and helped in all areas. All authors approved the final version of the manuscript.

How to Cite this Article:

Nissen M., Ikäheimo T.-M., Huttunen J., Leinonen V., Jyrkkänen H.-K., von und zu Fraunberg M. 2021. Higher Preimplantation Opioid Doses Associated With Long-Term Spinal Cord Stimulation Failure in 211 Patients With Failed Back Surgery Syndrome.
Neuromodulation 2021; 24: 102–111

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COMMENTS

Opioid use and escalation of dose is a major problem. This study explores the ability of electrical stimulation using electrodes implanted into the spinal cord to affect opioid use in patients with failed back surgery. The study is a retrospective analysis and the authors extracted data from the Finland health register and control data from the population register. The study shows that spinal cord stimulation was beneficial. It stopped opioid use in 20% of patients and reduced the escalation of opioid use. High opioid use appeared to compete with spinal cord stimulation, and the results suggest that electrical stimulation should be introduced early while opioid dose is low.

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The data from this study demonstrate a relationship between opioid tolerance and SCS los of efficacy. There could be many reasons for this parallelism varying from type of pain to psycho-social factors, to biological factors that should be analyzed by further studies.

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Pavia, Italy

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After revision this article became much clearer especially the message behind. as this is a retrospective analysis there are always some shortcomings, but the number of patients, the F-U time are making this article interesting creating some evidence on the negative effect of intake of opioids in chronic pain in general and especially in FBSS patients. This article is interesting to spread among insurance companies that prefer to reimburse back surgery without proper screening than SCS trial after careful medical/psychological screening.

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This prospective matched cohort study is a nice illustration of a key concept in neuromodulation in terms of factors that contribute to long-term SCS failure. As newer waveforms and accompanied evidence emerge, we are still troubled by the relatively high long term failure rates. The availability of opioid consumption data has allowed the authors to clearly show that high dose opioids prior to SCS trial can lead to poor long term outcomes. At the same time, this study does indicate the possible role SCS has in the reduction of opioids after successful implantation. The low 78% trial to perm ratio should encourage transition from 2 stage laminotomy paddle lead SCS to percutaneous SCS trials. I look forward to seeing how we can improve the accuracy of SCS trial process with emerging technologies such as closed-loop stimulation.

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