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Subcutaneous Stimulation as ADD-ON Therapy to Spinal Cord Stimulation Is Effective in Treating Low Back Pain in Patients With Failed Back Surgery Syndrome: A Multicenter Randomized Controlled Trial

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Objective: Suppression of back pain with traditional spinal cord stimulation (SCS) in failed back surgery syndrome patients is often insufficient. The objective of this study was to investigate the efficacy of subcutaneous stimulation (SubQ) as ADD-ON therapy to SCS in treating back pain in failed back surgery syndrome patients.

Materials and Methods: Patients with a minimal pain score of 50 on a 100 mm visual analog scale for both leg and back pain were eligible. If pain reduction after trial SCS was $\geq$50% for the leg but $<$50% for the back, patients received additional SubQ leads and were randomized in a 1:1 ratio in a study arm with subcutaneous leads switched on (SubQ ADD-ON) and an arm with subcutaneous leads switched off (Control). The primary outcome was the percentage of the patients, at three months since implantation, with $\geq$50% reduction of back pain.

Results: A total of 97 patients were treated with SCS for leg and back pain. Of these, 52 patients were randomized and allocated to the Control group ($n = 24$) or to the SubQ ADD-ON group ($n = 28$). The percentage of patients with $\geq$50% reduction of back pain was significantly higher in the SubQ ADD-ON group (42.9%) compared to the Control group (4.2%). Mean visual analog scale for back pain, at three months, was a statistically significant 28.1 mm lower in the SubQ ADD-ON group compared to the Control group.

Conclusion: Subcutaneous stimulation as an ADD-ON therapy to SCS is effective in treating back pain in failed back surgery syndrome patients where SCS is only effective for pain in the leg.

Keywords: chronic low back pain, failed back surgery syndrome, spinal cord stimulation, PNFS, subcutaneous stimulation

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INTRODUCTION

Failed back surgery syndrome (FBSS) is a chronic pain condition consisting of pain in the leg and/or the lower back after lumbar spinal surgery. Failure rates of lumbosacral spinal surgery range between 10% and 40% (1,2). While the pain in the leg is mainly neuropathic, due to radicular nerve damage, the cause of chronic low back pain (CLBP) is less obvious. It is often a mixture of neuropathic and nociceptive pain (3). Conventional medical management (CMM) in this group of patients is the first choice of treatment if indications for reintervention are absent. CMM includes nonsteroidal anti-inflammatory drugs, opioids, anticonvulsant and antidepressant drugs, epidural steroids, nerve blocks, psychological and physical rehabilitative therapy and transcutaneous electrical nerve stimulation (TENS) (4). If CMM fails, spinal cord stimulation (SCS) can be offered to the patients. The effectiveness of SCS in treating radicular pain caused by FBSS has been proven in several clinical studies (5–10). These studies however included mostly patients with predominant radicular leg pain. In this study we focus on patients with a more pronounced low back pain in addition to their leg pain.

Currently, these patients may be less suitable for SCS due to lower response rates over time (11–13). Case reports regarding the use of subcutaneous stimulation alone or as add on therapy to SCS in treating low back pain reported positive outcomes (14–18). A feasibility study performed by our group (15) showed a statistically significant reduction of pain in the leg and the lower back after 12 months of treatment with subcutaneous stimulation as add-on therapy to spinal cord stimulation in FBSS patients.

The results of this pilot study formed the basis for this efficacy study. We report on the outcomes of a randomized controlled trial in which we examined the efficacy of SubQ stimulation in treating CLBP in FBSS patients, already treated with SCS, at three months. We hypothesized that SubQ stimulation, as ADD-ON therapy to SCS, would be statistically significant better in treating CLBP in FBSS patients compared to SCS alone.

PATIENTS AND METHODS

Patients

The Multicenter Randomized Controlled Trial on the effectiveness of SubQ stimulation as an ADD-ON therapy for treating low back pain in FBSS patients recruited 100 patients in six centers in the Netherlands between November 2012 and July 2014. All patients signed an informed consent before the start of the study. Block randomization was centralized and eligible patients were assigned a treatment after informed consent and verification of baseline data. The protocol design was approved by an independent ethical committee (CMO Arnhem/Nijmegen: NL32464.091.10) and subsequently by the local ethical committees of the participating centers. The trial is registered at Clinical trials.gov (ID: NCT01776749).

Patients, between 18 and 75 years of age, suffering from neuropathic leg pain radiating in lumbosacral segments L4 and/or L5 and/or S1 combined with CLBP for at least six months after lumbar spine surgery, experiencing insufficient pain relief or unacceptable side effects with CMM were eligible for participating in this study.

Pain intensity, measured separately for legs and low back, had to be at least 50 mm on a 100 mm VAS line (where 0 means no pain and 100 mm indicates the worst possible pain) (19).

Patients were excluded if they suffered from another significant Chronic Pain Condition, Diabetes Mellitus, Ankylosing Spondylitis, Immune Deficiency, Lupus Erythematosus, a Coagulation Disorder, an active psychiatric disorder and an existing or planned pregnancy. Exclusion criteria also included the use of anticoagulants, which could not be temporarily withdrawn, drug or alcohol addiction, life expectancy of less then one year, a cardiac pacemaker, a history of SCS, a local infection or other skin disorder at the site of incision and an inability to operate the neuromodulation system.

Procedures

After informed consent and baseline measurements, patients were implanted with an epidural lead (Octad® lead model 3877, Medtronic, Minneapolis, MN, USA) and received trial stimulation intended to treat pain in back and leg. If, after trial stimulation, patients experienced $\geq$50% pain relief in their leg, but less than 50% pain relief in the lower back, they were randomized in a 1:1 ratio in two treatment arms and, in addition to the epidural stimulation, received one or two Quad® Plus Leads (Medtronic, Inc., Minneapolis, MN, USA) subcutaneously, depending on whether back pain was unilateral or bilateral.

Patients in the first treatment arm received no subcutaneous stimulation (Control) and patients in the second received optimal subcutaneous stimulation (SubQ ADD-ON) for a period of three months (Controlled phase). All patients were optimally treated with SCS for leg pain.

Treatment

SCS was performed as standard of care with an octopolar lead (Octad® lead model 3877, Medtronic, Minneapolis, MN, USA) according to the Dutch National Neuromodulation guidelines. When at least 80% of the painful area was covered with stimulation, the Octad® lead was fixated with a Titan®anchor (model 3550-39, Medtronic, Minneapolis, MN, USA) and connected with a temporary extension lead to an external neurostimulator (ENS, model 37022, Medtronic, Minneapolis, MN, USA). The duration of the trial stimulation period was at least one week. Depending on the effect of SCS on pain in the leg and lower back, the placement of the implantable pulse generator (IPG) was planned. The site of the IPG (Prime Advanced®, model 37702 or Restore Advanced®, model 37713, Medtronic, Minneapolis, MN, USA) was either marked on the left lower abdominal wall or on the left buttock. In case SCS was unsuccessful for treatment of CLBP, SubQ leads were implanted. The locations for placement of the right and left SubQ leads (Quad® Plus lead model 3888, Medtronic, Minneapolis, MN, USA) were precisely marked in the center of the painful area of the lower back with the patient in a upright position. Depending on the shape of the back pain area, the SubQ leads were placed in a vertical, horizontal or diagonal position. A bifurcated extension cable or a stretch coil extension cable (model 37082 and 37083, Medtronic, Minneapolis, MN, USA) was used to connect the Quad® leads to the IPG. A detailed description of the implantation techniques can be found in an earlier publication (15).

Each SubQ lead was programmed with its own bipolar configuration (Field stimulation). Stimulation frequency was set at a rate of 30 Hz, pulse width and amplitude were individually set to produce optimal stimulation/pain relief in the lower back. If field stimulation did not result in an optimal coverage of the painful area in the lower back, one SubQ lead could be programmed as anode, the other as a cathode (Flow stimulation) (20,21) or the SCS lead was programmed as anode and both SubQ leads as cathodes (Triangular stimulation) (22). Patients in the SubQ ADD-ON group were allowed to use SubQ stimulation 24 hours a day.

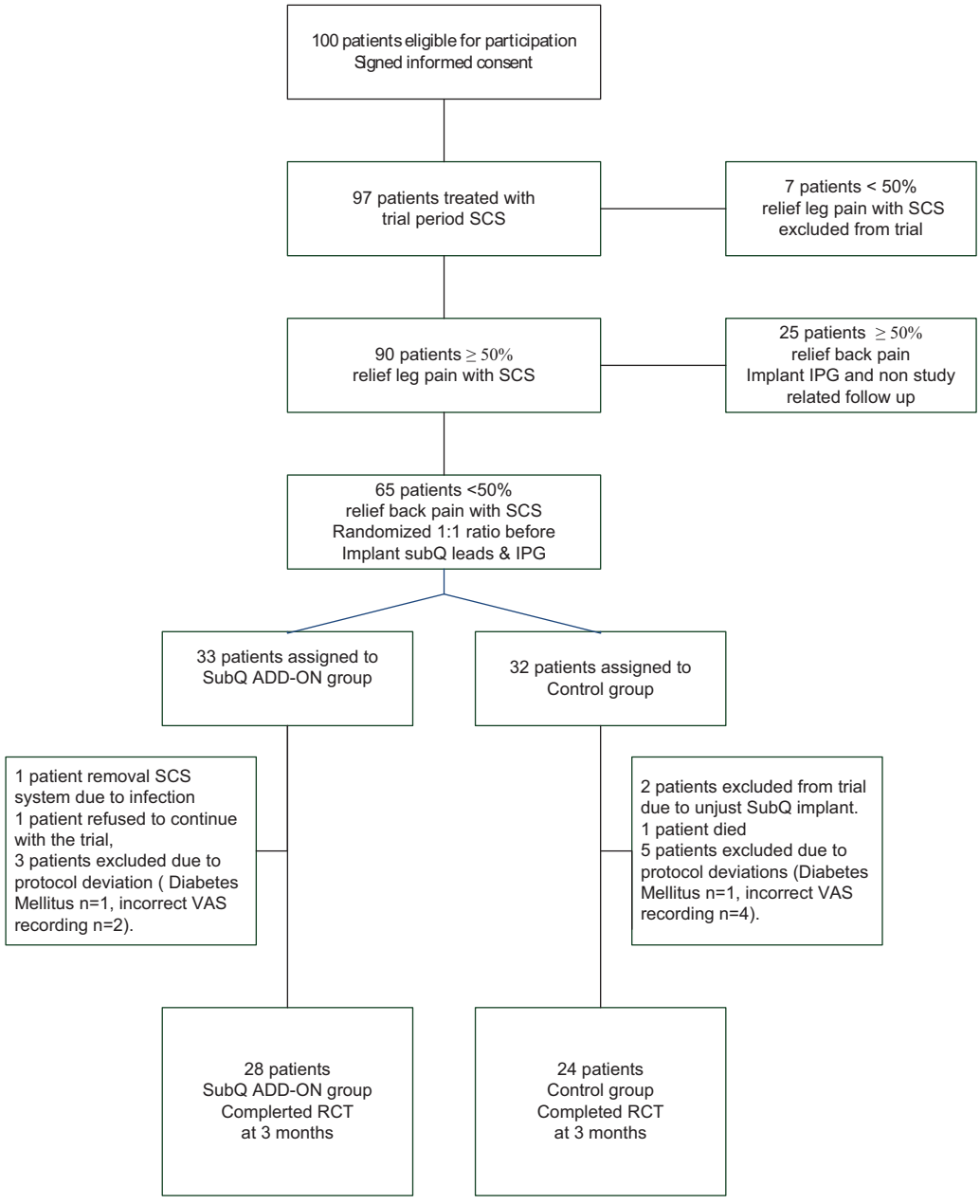

Figure 1. Flow diagram SubQ trial presents study design and patient flow at three months. In the SubQ ADD-ON group, five patients were excluded from trial participation versus eight patients in the Control group. Cause of death of one patient in the Control group was not study related.

Outcomes

The primary outcome was the proportion of patients having 50% or more relief of back pain measured on a 100 mm VAS line at three months since the start of stimulation.

Secondary outcomes included pain reduction in leg and back at three months assessed by using the McGill Pain Questionnaire Dutch Language Version (MPQ-DLV) (23), Quality of Life assessed by using the Medical Outcome Study-Short Form 36 (MOS-SF36) (24) and EuroQol (EQ-5D) (25,26), depression assessed using the Hospital Anxiety and Depression scales (HADS) (27), functionality assessed by using Oswestry Disability Index (ODI) (28,29), patient satisfaction assessed using the Patient Global Impression of Change (PGIC) (30), concomitant drug treatment for relief of pain by using the Medication Quantification Scale Version III (MQS-III) (31) and need for physical therapy or other nondrug treatment and employment status.

Statistical Methods

The primary outcome measure is the percentage of patients with $\geq$50% VAS back pain relief at three months since start of the stimulation. Based on the results of the feasibility study we assumed that the proportion of success patients in the SubQ ADD-ON group is 60% and in the Control group 20%. Then 28 patients are needed in each group to detect this difference with a power of 80% (Fisher-exact test, alpha = 0.05, 2-sided). As we take into account a potential loss to follow-up of about 10% and a success rate of 30% of SCS alone on leg and low back pain of included patients, we aimed to include 90 patients.

Baseline characteristics (age, gender, level of pain, etc.) are presented as median and range, or frequencies and percentages.

With respect to the primary outcome, Fisher-exact test was used to test the difference between the groups in the percentage of

Table 1. Baseline Characteristics of the Patients Included in This Study, by Group.

	SubQ ADD-ON ($n = 28$)		Control ($n = 24$)	
	n	(%)	*n*	(%)
Gender				
Male sex	19	(67.9)	13	(54.2)
Female sex	9	(32.1)	11	(45.8)
Leg pain				
Unilateral	22	(78.6)	17	(70.8)
Bilateral	6	(21.4)	7	(29.2)
Currently employed	3	(10.7)	1	(4.2)
	Median	(Range)	Median	(Range)
Age (years)	46.5	(33.0; 69.0)	53.5	(31.0; 73.0)
Number of surgeries	2.0	(1.0; 4.0)	2.0	(1.0; 9.0)
VAS legs	71.0	(50.4; 90.2)	72.5	(50.0; 95.0)
VAS Back	73.9	(50.4; 92.0)	73.0	(53.0; 92.5)

patients with ≥50% VAS back pain relief, for statistical significance. The estimated difference between the groups with the 95% confidence interval (CI) is presented. Similar analysis is performed, to study the difference in ≥50% VAS leg pain relief.

A linear mixed model was used to study the difference between the groups at three months since baseline for each of the secondary outcomes, separately. The dependent variable was the specific outcome of interest. The independent fixed variables were group (two levels: SubQ add-on, Control) and the baseline value. Center was treated as a random variable. We present the baseline-adjusted mean difference at three months with the 95% CI. The analyses were performed following the principle of intention-to-treat.

Statistical analyses were done using SAS 9.2 for Windows.

Study data were collected by means of an electronic web-based case report form (e-capture database, e-novex, Tielt, Belgium; www.e-capture.net).

RESULTS

In Figure 1, the flow diagram of the patients in the study is presented. Of 100 patients who signed informed consent, 97 were trialed with SCS with 90 patients reporting ≥50% pain relief in the legs after a period of trial stimulation. Of these 90 patients, 25 reported ≥50% additional pain relief in the lower back and after IPG implantation, they were included in a parallel group that had no part in the controlled phase of the study.

The group of 65 patients, who all reported ≥50% pain reduction in the legs but less then 50% pain relief in the lower back after trial stimulation, were randomized prior to implantation of SubQ leads and IPG, assigning 32 patients to the Control group and 33 to the SubQ ADD-ON group.

A total of 27 patients did not complete the first three months of the study. Three patients were excluded before trial stimulation could be performed due to cardiac problems ($n = 1$), an acute herniated lumbar disc ($n = 1$) and 1 patient was lost to follow up. In three patients, during implantation of the epidural lead, a minimum of 80% of the total pain area could not be covered by paresthesia. Four patients failed to achieve 50% pain reduction in the legs after trial stimulation. Three patients had their neuromodulation system explanted due to infection. One patient died during the first three months of the trial from a cause not related to the investigational treatment. A group of 14 patients were excluded from the study due to a variety of protocol violations, which included in-/exclusion criteria deviations ($n = 4$), incorrect assessment of pain intensity ($n = 9$) and an incorrect completion of a patient's questionnaire ($n = 1$). In the SubQ ADD-ON group 28 patients completed the controlled part of the study. In this group, 23 patients received two SubQ leads, five patients received just one SubQ lead, 12 patients had the IPG implanted in their abdominal wall and 16 patients in the upper outer quadrant of their left buttock. In the Control group 24 patients completed the controlled part of the study. In this group 22 patients received two SubQ leads, two patients received just one SubQ lead, 12 patients had the IPG implanted in their abdominal wall and 12 patients in the upper outer quadrant of their left buttock. The baseline characteristics of these patients (Table 1) are similarly distributed over both study groups.

The observed values of the primary and secondary outcomes by group by point of measurement and the estimated difference between the groups are presented in Table 2.

The percentage of patients with ≥50% VAS back pain relief at three months (primary outcome) is statistically significant higher in the SubQ add-on group compared to Control group (38.7 [95% CI: 18.7; 58.7]). In contrast, the percentage of patients with ≥50% VAS leg pain relief was nearly identical in both groups (0.6 [95% CI: −21.7; 22.8]).

Compared to patients in the Control group, patients in the SubQ ADD-ON group reported significantly lower levels of CLBP using the VAS ($p < 0.001$) and to a lesser extent by using the MPQ ($p = 0.121$). In the SubQ ADD-ON group, patients experienced improved health related quality of life on the EQ-5D ($p = 0.015$) and experienced an enhanced satisfaction with the therapy according to the patient global impression of change ($p = 0.036$). In the SubQ ADD-ON group, patients experienced less disability, measured with the Oswestry Disability Index, compared to patients in the Control group ($p = 0.068$). At three months, the Hospital Anxiety and Depression scales showed no difference compared to baseline in both groups.

The decrease in analgesic drug intake, assessed by using the MQS, was larger in the SubQ ADD-ON group compared with the Control group ($p = 0.238$).

Complications and Adverse Events

Of the 100 patients that were recruited in the trial, 65 were randomized in the two treatment arms. In these 65 patients, a total of 18 adverse events occurred within the first three months of treatment. One patient in the Control group experienced more than 1 event. There were 8 hardware related events, the most common being migration of the Octad®lead (4.6%) and Quad®lead (4.6%). Biological events included infection that required surgery (3.1%) or that could be treated with antibiotics (3.1%). Three patients complained about pain at the site of the IPG or connection site (4.6%). Two hematoma occurred, both superficial that needed no further intervention. There was 1 non-trial related death. In total, eight patients in the SubQ ADD-ON group (24.2%) and 10 patients in the Control group (31.3%) experienced at least 1 adverse event (Table 3). The occurrences of adverse events in the two study arms were not significantly different.

DISCUSSION

In this multicenter randomized controlled study, we found that subcutaneous stimulation of the low back region had a clinically and statistically significant effect on pain reduction compared to

Table 2. The Observed Values of Primary and Secondary Outcome Measures by Group, by Point of Measurement and the Estimated Difference Between the Groups at Three Months.

	Observed						Estimated		
	Baseline			Three months			Difference between groups at three months		
		n/N	(%)		*n/N*	(%)	Δ%	(95% CI)	*p* value
VAS back <50%[1] (number)									
SubQ add-on		NA			12/28	(42.9)	38.7	(18.7; 58.7)¥	0.001
Control		NA			1/24	(4.2)	0.0	(Ref)	
VAS legs <50%[1] (number)									
SubQ add-on		NA			6/22	(21.4)	0.6	(−21.7; 22.8)	1.000
Control		NA			5/24	(20.8)	0.0	(Ref)	
	n	Median	(Range)	*n*	Median	(Range)	Mean	(95% CI)	
VAS-Back (score 0–100)									
SubQ add-on	28	75.3	(7.6; 100.0)	28	44.8	(0.0; 82.3)	−27.2	(−39.7; −14.6)	<0.001
Control	24	68.9	(5.9; 91.0)	24	71.4	(31.0; 94.9)	0.0	(Ref)	
VAS-Legs (score 0–100)									
SubQ add-on	28	11.2	(0.0; 34.5)	28	13.7	(0.0; 64.3)	4.7	(−2.8; 12.2)	0.212
Control	24	8,3	(0.0; 78.0)	24	10,9	(1.4; 37.0)	0.0	(Ref)	
HADS (score 0–42)									
SubQ add-on	28	31.5	(26.0; 38.0)	28	31.5	(27.0; 42.0)	−0.1	(−1.6; 1.3)	0.884
Control	24	33.0	(26.0; 38.0)	24	32.0	(26.0; 39.0)	0.0	(Ref)	
Anxiety (score 0–21)									
SubQ add-on	28	15.0	(12.0; 20.0)	28	15.0	(12.0; 23.0)	0.2	(−0.8; 1.3)	0.649
Control	24	15.0	(11.0; 22.0)	24	15.0	(11.0; 19.0)	0.0	(Ref)	
Depression (score 0–21)									
SubQ add-on	28	17.0	(12.0; 22.0)	28	16.5	(11.0; 21.0)	−0.4	(−1.3; 0.6)	0.462
Control	24	16.0	(12.0; 22.0)	24	16.5	(14.0; 21.0)	0.0	(Ref)	
PGIC (score 1–7)									
SubQ add-on		NA		28	3.0	(1.0; 5.0)	−0.6	(−1.1; −0.0)	0.036
Control		NA		24	3.0	(2.0; 6.0)	0.0	(Ref)	
EQ5D									
SubQ add-on	28	0.2	(−0.1; 0.8)	28	0.8	(0.2; 1.0)	0.2	(0.0; 0.3)	0.015
Control	24	0.2	(0.1; 0.8)	24	0.6	(0.1; 0.8)	0.0	(Ref)	
Oswestry Disability Index									
SubQ add-on	28	60,0	(36.0; 82.0)	28	43.0	(8.0; 70.0)	−7.9	(−16.4; 0.6)	0.068
Control	24	58.0	(32.0; 72.0)	24	46.0	(24.0; 66.0)	0.0	(Ref)	
McGill Pain Questionnaire									
Pain ranking index affective									
SubQ add-on	28	6.0	(1.0; 11.0)	28	2.5	(0.0; 11.0)	−0.79	(−2.2; 0.6)	0.266
Control	24	3.5	(0.0; 12.0)	24	3.5	(0.0; 9.0)	0.0	(Ref)	
Pain ranking index evaluative									
SubQ add-on	28	8.0	(3.0; 10.0)	28	5.0	(0.0; 10.0)	−1.7	(−3.1; −0.3)	0.017
Control	24	8.0	(2.0; 12.0)	24	7.0	(3.0; 10.0)	0.0	(Ref)	
Pain ranking Index sensitive									
SubQ add-on	28	15.5	(3.0; 25.0)	28	7.5	(0.0; 27.0)	−1.9	(−5.1; 1.3)	0.236
Control	24	13.5	(0.0; 24.0)	24	10.0	(0.0; 22.0)	0.0	(Ref)	
Pain ranking Index total									
SubQ add-on	28	29.5	(12.0; 45.0)	28	17.0	(0.0; 45.0)	−4.2	(−9.6; 1.2)	0.121
Control	24	23.5	(11.0; 42.0)	24	20.5	(6.0; 36.0)	0.0	(Ref)	
Numerous word count									
SubQ add-on	28	14.0	(7.0; 20.0)	28	9.0	(0,0; 20.0)	−1.8	(−4.4; 0.7)	0.149
Control	24	13.0	(5.0; 18.0)	24	10.5	(4.0; 20.0)	0.0	(Ref)	
Short form-36									
SubQ add-on	28	47.5	(20.0; 92.0)	28	56.0	(15.0; 92.0)	−0.2	(−10.1; 9.8)	0.971
Control	24	48.5	(5.0; 82.0)	24	50.0	(30.0; 87.0)	0.0	(Ref)	
Role-Phys.									
SubQ add-on	28	0.0	(0.0; 50.0)	28	0.0	(0.0; 100.0)	6.8	(−12.6; 26.1)	0.486
Control	24	0.0	(0.0; 25.0)	24	0.0	(0.0; 100.0)	0.0	(Ref)	
Health									
SubQ add-on	28	25.0	(0.0; 50.0)	28	75.0	(0.0; 100.0)	13.9	(0.4; 27.4)	0.043
Control	24	25.0	(0.0; 75.0)	24	75.0	(0.0; 100.0)	0.0	(Ref)	

Table 2. *Continued*

	Observed						Estimated		
	Baseline			Three months			Difference between groups at three months		
		n/N	(%)		*n/N*	(%)	Δ%	(95% CI)	*p* value
Pain									
SubQ add-on	28	22.0	(0.0; 41.0)	28	41.0	(0.0; 100.0)	12.5	(1.0; 24.1)	0.033
Control	24	22.0	(0.0; 41.0)	24	32.0	(0.0; 74.0)	0.0	(Ref)	
vitality									
SubQ add-on	28	35.0	(10.0; 75.0)	28	40.0	(10.0; 100.0)	7.2	(−3.9; 18.2)	0.198
Control	24	45.0	(20.0; 90.0)	24	47.0	(15.0; 85.0)	0.0	(Ref)	
Social									
SubQ add-on	28	37.5	(0.0; 75.0)	28	50.0	(0.0; 100.0)	8.7	(−6.7; 24.1)	0.263
Control	24	31.3	(0.0; 75.0)	24	50.0	(0.0; 100.0)	0.0	(Ref)	
Role emot.									
SubQ add-on	28	66.7	(0.0; 100.0)	28	100.0	(0.0; 100.0)	−2.5	(−27.0; 21.9)	0.835
Control	24	100.0	(0.0; 100.0)	24	100.0	(0.0; 100.0)	0.0	(Ref)	
Mental									
SubQ add-on	28	68.0	(28.0; 92.0)	28	72.0	(32.0; 100.0)	7.1	(−2.1; 16.4)	0.129
Control	24	68.0	(32.0; 96.0)	24	66.0	(24.0; 100.0)	0.0	(Ref)	
MQS III									
SubQ add-on	28	11.0	(0.0; 46.5)	28	8.7	(0.0; 39.7)	−2.06	(−5.5; 1.4)	0.238
Control	24	13.5	(2.3; 31.2)	24	15.5	(0.0; 31.2)	0.0	(Ref)	

1, compared to baseline, that is, >50% improved. NA, Not applicable. ¥, Primary outcome. Ref, reference value. Group differences were estimated using a linear mixed model with adjustment for baseline and cluster, in case of continuous outcomes. VAS: 0 means no pain, 100 means worst possible pain, HADS: Scores of 0–7 indicate normal levels of anxiety/depression; 8–10 indicates borderline anxiety/depression levels and 11–21 suggest abnormal levels of anxiety/depression. PGIC: Patient global impression of change (1 = complete recovery; 7 complaints worse than ever before), SF-36: 0 means maximum disability and a score of 100 means no disability, ODI: 0 means no disability, 100 means maximum disability.

patients treated with SCS alone. Twelve patients (42.9%) in the intervention group (SubQ ADD-ON) achieved pain reduction in the back of 50% or more compared to only 1 patient (4.2%) in the Control group. VAS scores of CLBP at three months were compared with VAS scores at the end of trial period, to show the additional pain-reducing effects of SubQ on CLBP, in FBSS patients already treated with SCS. This finding is consistent with the results of the feasibility study by Hamm et al. (15).

Table 3. Adverse Events and Complications Within Three Months of the Patients Randomized in This Study by Group and Total.

Event etiology	Sub ADD-ON (*n* = 33)	Control group (*n* = 32)	Total
Hardware related problems	3	5	8
Octad lead failure		1	1
Octad lead migration	1	2	3
Quad lead failure	1		1
Quad lead migration	1	2	3
Biological complications	5	4	9
Infection requiring surgery	1	1	2
Infection requiring antibiotics	1	1	2
Pain at IPG site	2		2
Pain at connection site	1		1
Haematoma		2	2
Death		1	1
Total	8	10	18

The (serious) adverse events in the two randomized SubQ groups within three months. One patient in the control group experienced two adverse events, that is, quad lead migration and a hematoma.

Chronic low back pain in FBSS patients has always been considered as being difficult to treat with SCS and attention was mainly directed at reducing the neuropathic leg pain (32–34). Traditionally, for SCS to be effective, the painful area of the leg and lower back had to be covered by paresthesia by electrically stimulating the dorsal columns with an epidurally placed lead (1,35). According to the gate theory by Melzack and Wall, stimulation of thick Aβ-fibers in the dorsal columns could block pain-signals mediated by peripheral C-fibers (36). Although the gate theory is widely accepted, the exact mechanisms of SCS are still unclear. Difficulties with achieving and maintaining adequate and long-term pain relief of CLBP were often reported (3,8,11,13). Changes in pain patterns, lead migration, changes in the patterns of stimulation and the inability to place the epidural lead in the physiologic midline have all contributed in failing to achieve long-lasting relief of CLBP with SCS. Therefore, the presence of predominant low back pain in FBSS patients was, for a long time, regarded to be a risk factor that could jeopardize the outcome of SCS (32,33).

In the last decade, the use of SCS for treating leg and low back pain in FBSS patients has increased, due to improvements in lead design, electrode arrays and programmable pulse generators. Barolat used surgical leads (2 × 8 electrodes) and concluded that the effect on back pain was more than 50% after 12 months (5). North compared a four electrode epidural lead with a 2 × 8 surgical lead (35) and found no technical advantage in using more electrodes to increase the region of paresthesia. Epidural stimulation with a percutaneously introduced paddle lead to treat low back pain in patients with FBSS resulted in coverage of the back pain area in 85% of the patients and a pain reduction of 52% after one year (37). For treating leg and back pain in FBSS patients with conventional tonic SCS, thus replacing painful stimuli with pleasant paresthesia in that same area

of pain, the use of two epidural leads or a surgical paddle leads have become standard of care over the past few years. The presence of paresthesia in SCS however, does not seem necessary for a pain suppressive effect. By increasing the frequency to 10 kHz, pain relief can occur without paresthesia (38,39). In a randomized, non-inferiority study, Kapural compared traditional SCS with paresthesias with 10-kHz SCS in a patient group with back and/or leg pain. In this study, 84.5% of patients in the 10-kHz SCS group experienced a reduction of back pain $\geq$50% vs. 43.8% of patients in the control group. These effects were sustained at 12 months follow up and based on the results of this study 10-kHz SCS seems a very promising therapy for treating back and leg pain in FBSS patients (40). SCS at 500 Hz in bursts of five rapid pulses delivered in a rate of 40 Hz is also able to produce pain relief with a minimum of paresthesia (41,42). The exact mechanisms of action of these paresthesia-free types of SCS are also poorly understood.

For our study, we have chosen to treat FBSS patients with leg pain and substantial back pain with a combination of traditional SCS and PNFS. SCS is an approved therapy for treating neuropathic limb pain in FBSS patients which is minimal invasive, safe and cost-efficient in a selected group of patients (11,43,44). PNFS was used as an additional therapy when SCS alone was not sufficient in treating back pain. Subcutaneous implantation of electrical leads has some major advantages over placing leads in the epidural space. There is no risk of dural puncture or epidural bleeding. Also a subtle migration of the subcutaneous lead will not result in loss of effect as is seen with epidural leads. The Prime Advanced® (Medtronic, Minneapolis, MN, USA) and Restore Advanced® (Medtronic, Minneapolis, MN, USA) are both IPG's capable of stimulating 16 different electrodes. Using a maximum of two subcutaneous Quad®Plus (Medtronic, Minneapolis, MN, USA) leads combined with an Octad® electrode (Medtronic, Minneapolis, MN, USA) for SCS, it is possible to cover not only the leg and buttock but also a large area of the lower back with stimulation with the power of just one IPG. As with SCS, the exact mechanism of action of PNFS remains unclear. Implanting additional subcutaneous leads will prolong the duration of surgery and might lead to an increase in surgical site infections. The infections rate within the first three months of this trial however did not exceed that of what is known from several SCS studies (4.0–10%) (45) as was the case with hardware related events, such as lead migration or failure (46,47).

This trial design has several strengths. First, it is a multicenter, prospective study with equally sized treatment arms and it has the presence of a control group. Second, for our primary outcome on back pain, we determined clinical significant pain relief as having $\geq$50% pain reduction on a weighted VAS. This allows for the results to be compared with previous studies that have the same definition of success rate.

The design of this trial also has some limitations. First, the Ethics Committee did not allow the randomized phase to be longer than three months, because, in their opinion, it would be unethical to provide patients with a therapy capable of diminishing pain that remains inactivated for a longer period and hence providing no pain relief. Second, an important limitation of the techniques used in this study is the fact that patients cannot be blinded. SCS and SubQ are techniques in which electrical current depolarizes the thick Aβ-fibers in the dorsal column and thereby blocks the pain-signals mediated by the C-fibers coming from the periphery (Gate theory of pain). As a result patients who receive SCS/SubQ feel paresthesia and this phenomenon does not allow blinding of patients. At the time the protocol was designed, subthreshold stimulation or high frequency (10 K) stimulation were not well-known established therapies. McRoberts et al. (48) reported on the efficacy and safety of PNFS in FBSS patients with intractable back pain. In this study they compared four groups of stimulation (minimal, subthreshold, low frequency, and standard stimulation). Patients with standard stimulation showed the best improvement for all pain variables and SF-36 while the least favorable response was seen in the sub threshold group. The effects of high frequency SubQ have not been reported yet.

CONCLUSION

Subcutaneous stimulation as an ADD-ON therapy to Spinal Cord Stimulation is an effective therapy in treating low back pain in FBSS patients in whom traditional Spinal Cord Stimulation alone is only effective for radiating pain in the leg. This study presents the first evidence that subcutaneous stimulation can be effective in treating low back pain in FBSS patients. We expect this to be a long-term effect and the results of the 12 months follow up are soon to be analyzed.

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Authorship Statement

Study design was performed by Drs. Gultuna, Aukes, Spincemaille, Teernstra, Vonhögen, Vissers and Mrs. Hamm-Faber. Patient recruitment and data collection were completed by Drs. Van Gorp, Gultuna, Aukes, Burger, Kallewaard, Vonhögen, Schapendonck and Teernstra. Dr. Hendriks performed statistical analysis. Dr. Van Gorp prepared the manuscript draft with important intellectual input from Drs. Teernstra, Spincemaille, Hendriks and Vissers. The manuscript draft was corrected and completed by Drs. Gultuna, Burger, Schapendonk, Kallewaard, Vonhogen and Mrs. Hamm-Faber. All authors approved the final manuscript.

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COMMENTS

This study is important because it confirms the usefulness of subcutaneous stimulation (or peripheral nerve field stimulation, PNfS) as an adjunct to spinal cord stimulation (SCS). The implanting surgeon should be aware that, if unable to reach the lumbar area with SCS, subcutaneous stimulation could safely be added either at the same implant or as a later revision/implant. With the combination of SCS and PNfS one can assure the patient that the desired areas of the low back can ALWAYS be covered. The protocol utilized in this study, with one single epidural octopolar percutaneous lead might not be the optimal construct to stimulate the lumbar area. However, even with the most sophisticated constructs/waveforms/frequencies there will always be some patients who just do not experience pain relief in the lumbar area. In those instances, PNfS is a very welcome tool in the armamentarium of the implanting physician.

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This study is another important step in validating that appropriately utilized peripheral nerve field stimulation can be advantageous in treating low back pain associated with failed back surgery syndrome. Additionally what it confirms is that again, traditional, tonic stimulation is challenged with providing low back coverage (25/90 patients with >50% pain relief of the low back). It confirms that the addition of PNfS, while not powered to compare adverse events, does not show statistical increase of adverse events. The anecdotal weakness of PNfS, despite sustained relief at one year in our prospective study, is that efficacy wanes over time; this early data does not yet speak to that. This is a good effort at further confirming the value of PNfS. Longer data will be welcome, and competitive treatments, high frequency, surging-type stimulation patterns and even dorsal root ganglion stimulation (DRG) need to further evaluation for low back pain treatment, especially as compared to PNfS. My suspicion is that PNfS is and will remain a particularly safe and hopefully viable option for focused pain loci, especially axial pain and as the aim of axial pain treatment moves cephalad, PNfS may remain the best treatment option. Our patients will benefit greatly from the coming evaluations.

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Comments not included in the Early View version of this paper.

