Observational Study

24-month Real-World Study of Spinal Cord Stimulation in Failed Back Surgery Patients with Refractory Pain

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Background: Failed Back Surgery Syndrome (FBSS) causes disability and lowers health-related quality of life (HRQoL) for patients. Many patients become refractory to Conventional Medical Management (CMM) and Spinal Cord Stimulation (SCS) is advised. However, comparative effectiveness research of both clinical approaches still lacks further evidence.

Objectives: This study describes Comparative Effectiveness Research of CMM versus SCS to provide real world evidence regarding the appropriate means for FBSS management, in terms of Patient-Reported Outcomes Measures.

Study Design: Naturalistic, pragmatic, prospective observational multicenter SEFUDOCE-study

Setting: FBSS patients attending clinical programmed visits in Pain Unit at Hospital Universitario de La Princesa and at Hospital General Universitario de Alicante (Spain).

Methods: Study evaluates the impact on pain, functional limitation, and HRQoL of CMM versus SCS in the management of FBSS. Patients completed Pain Detect Questionnaire, Oswestry Disability Index, EQ-5D-3L, Medical Outcomes Study Sleep Scale, and Hospital Anxiety and Depression Scale at baseline and at 3, 6, 12, 18 and 24 months. Longitudinal data were analysed with repeated-measures one-way analysis of variance adjusting by confounders.

Results: Eighty-five adults patients with FBSS receiving treatment according to current clinical practice were assessed. After 24 months, the PainDETECT Questionnnaire showed that CMM patients maintained similar scores, while SCS patients reduced their overall score (current pain: 6 CMM versus 4.21 SCS, $P = 0.0091$; intensity strongest pain: 7.77 CMM versus 6.07 SCS, $P = 0.0103$; average pain: 6.46 CMM versus 4.75 SCS, $P = 0.0012$). For the Oswestry Disability Index, the Medical Outcomes Study Sleep Scale, and the Hospital Anxiety and Depression Scale no significant inter-group differences were found. EQ-5D utility improved in SCS patients from baseline (baseline: 0.32 CMM versus 0.22 SCS; 24-month: 0.37 CMM versus 0.63 SCS, $P = 0.026$). Twenty-four month follow-up showed unlikely presence of neuropathic pain and moderate disability in SCS patients, whereas the CMM patients maintained baseline health state.

Limitations: Given the nature of the intervention, conducting a blinded study was not considered practically feasible. A larger sample could also overcome having younger patients in the SCS arm.

Conclusions: SCS may improve the HRQoL and functionality of FBSS patients with refractory pain in the long-term compared to CMM alone.

Key words: Chronic pain management, conventional medical management, failed back surgery syndrome, observational study, spinal cord stimulation

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Failed Back Surgery Syndrome (FBSS) incidence ranges from 10% - 40% after lumbar laminectomy (1-3) and 19% following lumbar microdisectomy (1,2). Pain is not only an impediment to leading a full life, but when pain becomes chronic -as in FBSS patients- insomnia, anxiety, severe disability, and social isolation frequently come along (2,4,5).

Lower-back pain has become a common health problem as evidence by the current high number of lumbar surgeries (6-8), underlining the need for complete knowledge of proper FBSS management. However, there is a paucity of clear FBSS treatment guidelines (2,5) and due to the variety of types of pain involved (nociplastic, neuropathic, nociceptive, etc.), an interdisciplinary multimodal approach of different therapies is required (9-11).

Conventional Medical Management (CMM) involves a wide range of pharmacological treatment (1,5,8) and also includes facet joint procedures, adhesiolysis, disc interventions, physical therapy, and psychological therapy (7). Many patients become refractory to CMM. Nonpharmacological approaches are associated with short-term pain relief and improvements in functioning (2).

Spinal Cord Stimulation (SCS) has been introduced as a complementary treatment for those chronic patients, when neuropathic pain components are present (7,12-15). There is evidence that SCS is an effective treatment for FBSS (12,13,16,17) as the stimulation of large-diameter afferent nerve fibers, with subsequent changes in adenosine, serotonin, and substance P levels can produce an inhibitory effect on pain sensation (7,14). SCS also improves quality of life in FBSS patients (12). Given these advantages, SCS seems underused (18).

The objective of this study was to compare CMM versus SCS for FBSS management in terms of Patient-Reported Outcomes Measures (PROMs).

Methods

The SEFUDOCE (Cost-Effectivity of Pain Unit for Failed Back Syndrome)-study is an open, observational, prospective study of a single cohort implemented to assess the costs and effectiveness of treatment of pain secondary to FBSS. This study aims to respond to the lack of prospective studies in Spain that value the cost of the different treatments used for the treatment of back pain secondary to FBSS and to the lack of prospective data demonstrating the effectiveness of these therapies used over time. The STROBE recommendations were followed(19).

The naturalistic, pragmatic, prospective observational SEFUDOCE-study was conducted in FBSS patients attending clinical programmed visits in Pain Unit Stage IV at Hospital Universitario de La Princesa and at Hospital General Universitario de Alicante (Spain) according to the current clinical treatment approaches.

Inclusion criteria: (1) patients aged ≥ 18, (2) diagnosed with secondary pain related to FBSS, (3) able to properly understand and speak the Spanish language, (4) patients newly sent to the Pain Unit.

Exclusion criteria: (1) patients with pain not related to FBSS, (2) unable to answer the questions due to their educational level or to a psychiatric or neurological disorder, (3) whose clinical data could not be obtained.

The protocol of the SEFUDOCE-study was approved by the Ethics Committee of Hospital Universitario de la Princesa and carried out in full observance of the Ethical Principles for Medical Research Involving Human Subjects (WMA Helsinki). All patients provided written informed consent before enrollment.

Patients were assessed between 2011 and 2015 to complete a 24-month observational period. Patients enrolled in the 2 groups had been previously treated according to common practice. Once the patients arrived to the Pain Unit, an initial examination was done and sociodemographic variables were analyzed. In the following 2 weeks, , patients were assigned to either the CMM or the SCS arm based on clinical criteria evaluated by a multidisciplinary meeting with UDOC members. Patients were asked to fill out 5 PROMs. The same PROMs were readministered at months 3, 6, 12, 18, and 24 (Fig. 1).

Procedure

CMM included oral and intravenous pharmacological treatment, such as antiinflammatory drugs, analgesics, opioids, muscle relaxants, anticonvulsants, and dual or tricyclic antidepressants. Physical therapy, nerve block and trigger point block, epiduroscopy, radiofrequency, epidural procedures, and oxygen-ozone therapy were performed for the discs and muscles. The SCS patients were then implanted with a rechargeable system, with an estimated battery life of at least 12 years and were programmed at baseline. Eighty-three percent of patients were programmed with conventional SCS (Tonic stimulation: 40 - 70 Hz; 280 - 420 microsec; 3,8 - 6 mA) and 17% with high-frequency stimulation (1000 Hz; 200 microsec; 2 mA). Concurrently, all tonic patients added simultaneous subthreshold stimulation programs (Burst (6 pulses) and/or high frequency) based on the patient's discretion. Patients first received an SCS trial for 1 to 2 weeks. If patients reported ≥ 50% pain reduction, permanent SCS systems are implanted.

SCS patients were also offered pharmacological treatment, and the use of medication was monitored during the trial period.

Outcome Measures

PROMs have proved to be reliable and responsive measures for a thorough assessment of symptoms and Health-Related Quality of Life (HRQoL) in patients worldwide (20-22). PROMs used in our study were PainDETECT Questionnaire (PD-Q), Oswestry Disability Index (ODI), Medical Outcomes Study Sleep Scale (MOS-SS), Hospital Anxiety and Depression Scale (HADS), and EQ-5D-3L (23-26).

Statistical Analysis

Parametric tests were used in case fit assumptions. Otherwise, nonparametric analysis were performed. Longitudinal data were analysed with repeated measures Anova adjusting by confounders (gender, age, number of previous surgeries, years since diagnosis, and symptomatology) to identify whether there were significant improvements in scores, through the monitoring of visits for each test. Missing data was not addressed. Analyses were performed using R 3.5.1 software, and a critical *P*-value of 0.05.

Results

Study Population

Eighty-five patients were admitted for research (Per Protocol): 46 patients in the CMM arm (54.12%) and 39 in the SCS arm (45.88%) (Fig. 1). The percentage of FBSS patients who completed a 1 year follow-up out of the total sample at baseline was 71.76% (32.94% CMM versus 38.82% SCS) and 63.53% for the 2 year follow-up (27.06% CMM versus 36.47% SCS). The loss of follow-up information was greater in the CMM group at every monitored visit, except at month 24 when compared to the SCS group and was signicantly greater at months 12 ($P = 0.0291$), 18 ($P = 0.0024$) and 24 ($P = 0.0096$). Two patients from the CMM arm underwent a neurostimulator implant (after 1 month and 10 months monitoring, respectively) and 3 patients from the SCS group needed minor reoperations. In accordance with ITT principles of analyses, initial group allocation was maintained throughout.

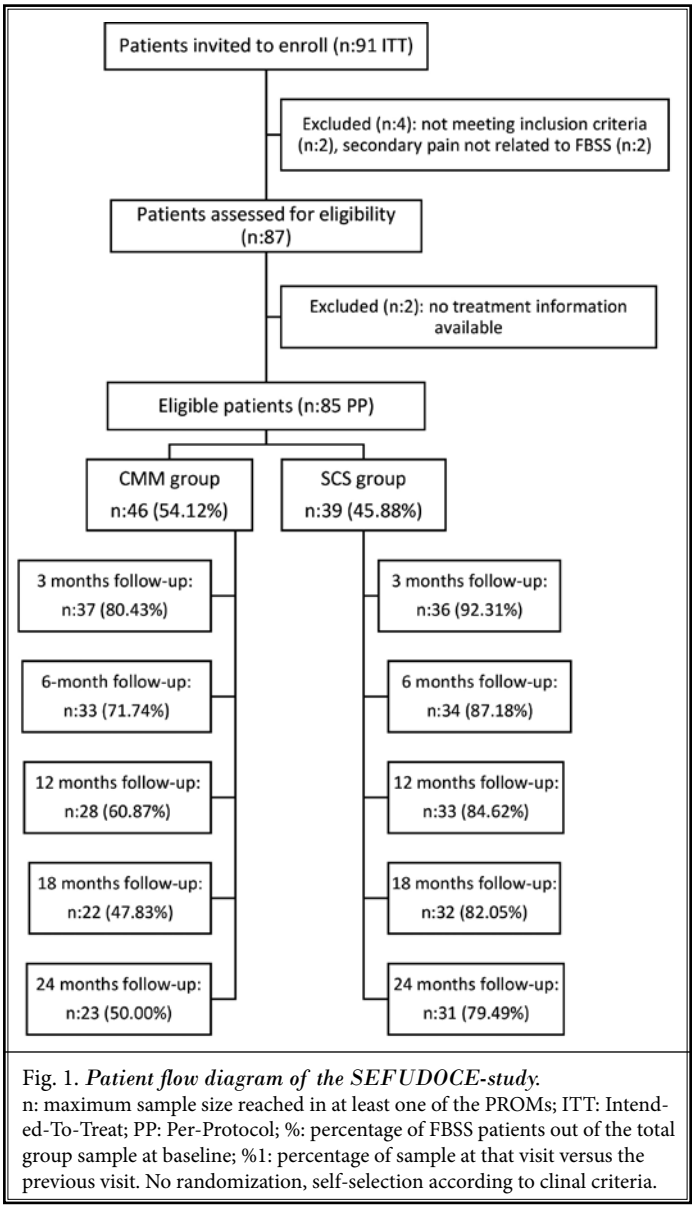

Fig. 1. *Patient flow diagram of the SEFUDOCE-study.*
n: maximum sample size reached in at least one of the PROMs; ITT: Intended-To-Treat; PP: Per-Protocol; %: percentage of FBSS patients out of the total group sample at baseline; %1: percentage of sample at that visit versus the previous visit. No randomization, self-selection according to clinal criteria.

Demographics

The proportion of women was significantly higher in the CMM group ($P = 0.0168$). The SCS patients were significantly younger (7 years, $P = 0.0025$) and had a significantly higher number of back surgeries ($P = 0.0102$). The highest numbers of previous surgeries were recorded for arthrodesis, hemilaminectomy, and laminectomy. Of the patients treated with neurostimulation, 97.37% had low back pain in comparison with 82.22% of those receiving a conventional treatment ($P = 0.063$) and radiculopathy was 89.47% and 82,22%, respectively ($P = 0.53$). No significant differences were found between the groups for current state of anxiety and depression, number of years

since diagnosis, and symptomatology, presence and location of low back pain, and radiculopathy. Risk factors assessment indicated that the SCS group had a statistically significant higher risk percentage in the hepatobiliary system than the CMM group (P = 0.0349) (Table 1).

Table 1. *FBSS patients characteristics per arm.*

Characteristics	CMM group		SCS group		
	n (%)	Mean (SE)	n (%)	Mean (SE)	*P*-value
Age (y)	46 (100)	60.78(b) (1.82)	39 (100)	53(b) (1.81)	
Female	37(a) (80.43)		21(a) (53.85)		
Educational attainment					0.6730
No formal education	1 (2.17)		0 (0)		
Primary education	18 (39.13)		14 (35.90)		
Lower secondary education	12 (26.09)		10 (25.64)		
Upper secondary education	7 (15.22)		10 (25.64)		
Higher education	8 (17.39)		5 (12.82)		
Employment status					0.2839
Active	10 (21.74)		11 (28.21)		
Unemployed	8 (17.39)		5 (12.82)		
Stay-at-home	9 (19.57)		3 (7.69)		
Temporary disability	0 (0)		1 (2.56)		
Work absence due to disability	7 (15.22)		11 (28.21)		
Retired	12 (26.09)		7 (17.95)		
Refused/Don't know	0 (0)		1 (2.56)		
Presence of risk factors					
Cardiovascular system	17 (36.96)		10 (25.64)		0.3773
Digestive system	11 (23.91)		10 (25.64)		1.0000
Respiratory system	6 (13.04)		4 (10.26)		0.9525
Hepatobiliary system	1(a) (2.17)		7(a) (17.95)		0.0349
Endocrine system	14 (30.43)		10 (25.64)		0.8045
Inmune system	4 (8.70)		2 (5.13)		0.8298
Musculoskeletal system	14 (30.43)		14 (35.90)		0.7624
Depression and Anxiety					0.7322
Anxiety	2 (4.35)		0 (0)		
Depression	3 (6.52)		1 (2.56)		
Drug consumption					
Opioids	19 (39.58)		31 (79.49)		0.0004
Sedatives	12 (25.00)		11 (28.21)		0.9261
Anticonvulsants	16 (33.33)		21 (53.85)		0.0879
Antidepressants	9 (18.75)		9 (23.08)		0.8186
Others					
Years since diagnosis	44 (95.65)	6.77 (0.73)	36 (92.31)	8.03 (0.92)	0.3295
Years since onset of symptoms	44 (95.65	8.16 (0.87)	37 (94.87	9.22 (1)	0.4356
Number of previous low back surgeries	46 (100)	1.37(a) (0.08)	38 (97.44)	1.76(a) (0.12)	0.0102
Presence of low back pain	38 (82.61)		38 (97.44)		0.069
Presence of radiculopathy	38 (82.61)		35 (89.74)		0.5295

CMM: conventional medical management; SCS: spinal cord stimulation; (a) $P \leq 0.05$; (b) $P \leq 0.01$.

PainDETECT Questionnaire (PD-Q)

The inter-group difference among PD-Q average scores was statistically significant at the initial examination: 14.56 points for the CMM arm and 19.49 for the SCS arm (P = 0.0008). The SCS arm reported likely presence (> 90%) of neuropathic pain components at baseline. At the 24-month monitored visit, the SCS average score fell to 9.3 (reduction of 10.19 points), compared to a reduction of 0.48 points (to 14.08) for the CMM arm, at which point there was no statistically significant difference between the groups mean scores (P = 0.0509) (Table 2, Fig. 2b). Regarding intra-group differences, the CMM arm achieved a reduction of 0.64 points, while the SCS arm got a significant 9.79-point drop (P = 0.0000) (Table 2). SCS patients showed unlikely evidence (< 15%) of neuropathic pain components at 24-months. These improvements reflected changes reported in: pain at the present moment, strongest pain in the past month, average intensity of pain in the past month, burning sensation, light touching, numbness sensation, and pain felt by slight pressure (Fig. 3). Of the SCS patients 58.97% and 15.22% of the CMM patients showed a significant reduction of 30% of the PD-Q total score (P < 0.001), in comparison to baseline self-reported state. Also, a statistically significant reduction of 30% was detected in pain at the present moment (11% CMM versus 51% SCS; P < 0.001), strongest pain in the past month (2% CMM versus 41% SCS; P < 0.001), average intensity of pain in the past month (9% CMM versus 51% SCS; P < 0.001). Of the SCS patients 48.72% and 8.7% of the CMM patients acihieved a reduction of at least 50% (P < 0.001) . Significant reduction of 50% was detected in pain at the present moment (4% CMM versus 36% SCS; P < 0.001), strongest pain in the past month (0% CMM versus 23% SCS; P < 0.001), and average intensity of pain in the past month (0% CMM versus 18% SCS; P < 0.01).

Regarding patients follow-up evolution, the CMM PD-Q average score showed an irregular trend, reporting the lowest scores at months 12 and 18. The SCS arm showed a downward tendency, registering lower scores almost consecutively in each follow-up visit, up to month 24. SCS patients stopped showing likely evidence of neuropathic pain components after 6 months of monitoring. Differences between trends over time followed by the 2 groups of patients were statistically significant (P = 0.00), due to time by treatment effects (treatment effects and time effects altogether, P = 0.00). This means that over time, both group of patients perceived changes in their health state, but the SCS arm showed a steady decrease.

Table 2. *Patient-Reported Outcome Measures (PROMs) baseline compared to 24-month follow-up.*

PROMs	Baseline vs 24-month follow-up outcomes					
	CMM group		SCS group		Inter-group differences* (CMM outcomes – SCS outcomes)	
	n	Intra-group differences (24-month outcomes – baseline outcomes)	n	Intra-group differences (24-month outcomes – baseline outcomes)	Differences at baseline	Differences at 24-month visit
PD-Q total score	25	-0.64	33	-9.79(c)	4.93†	-4.78
Pain at present moment	23	-0.52	29	-3.31(c)	0.83(a)	-2.05(b)
Strongest pain during the past 4 weeks	23	-0.7(a)	29	-3.34(c)	0.63(b)	-2.22(c)
Average pain intensity during the past 4 weeks	23	-0.48	29	-2.76(c)	0.43	-2.02(c)
ODI Total score	25	-6.47	33	-23.25(c)	8.5	-8.52
EQ-5D-3L utility (Spanish value set)	23	-0.01	30	0.39(c)	-0.1	0.29(b)
EQ- VAS	23	12.39(a)	30	24.97(c)	3.74	19.17(b)
MOS-SS 6 dimensions	23	-0.72	30	-12(c)	9.07	0.78
MOS-SS 9 dimensions	22	-0.88	30	-13.35(c)	9.55(a)	-3.3
HADS total score for anxiety	23	-5.61(c)	26	-5.77(c)	0.76	0.6
HADS total score for depression	23	-5.17(c)	28	-5.85(c)	1.19	0.51
HADS global score	23	-10.78(c)	26	-11.62(c)	1.94	1.11

* Positive differences mean that the SCS patients scored higher at the corresponding scale. (a) $P \leq 0.05$; (b) $P \leq 0.01$, (c) $P \leq 0.001$.

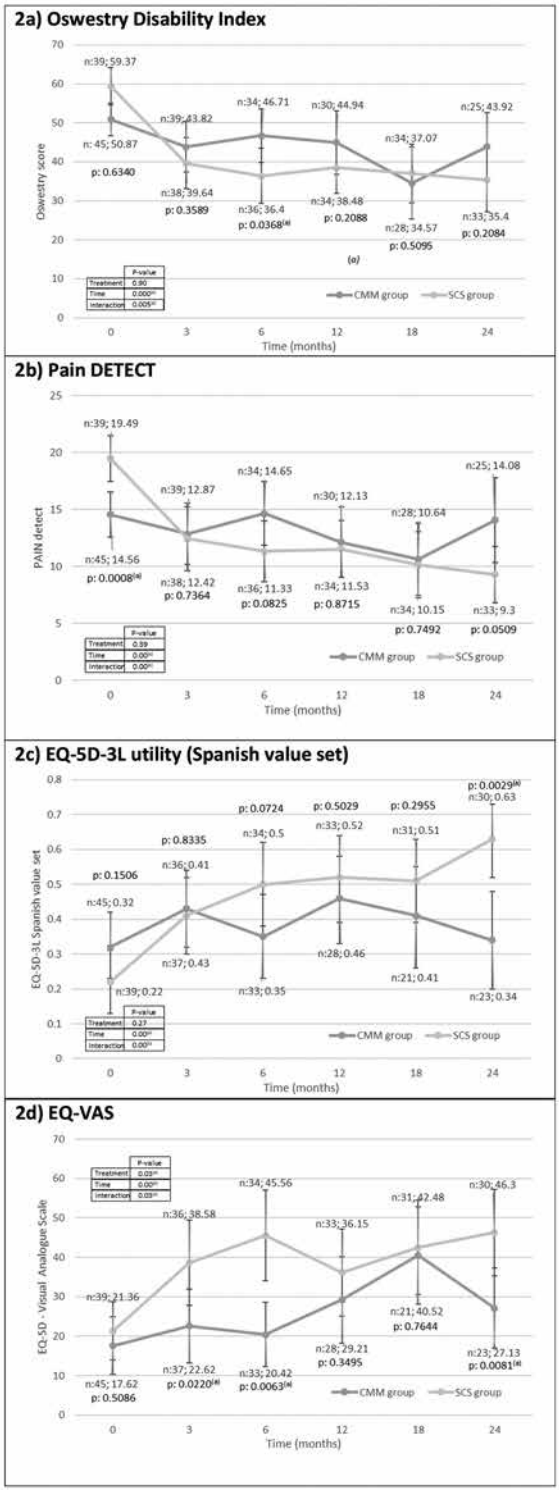

Fig. 2. *Evolution of the Oswestry Disability Index, the pain DETECT, the EQ-5D-3L utility (Spanish value set) and the EQ-VAS average scores for each treatment arm.*
CMM: conventional medical management; SCS: spinal cord stimulation; (a) $P \leq 0.05$.

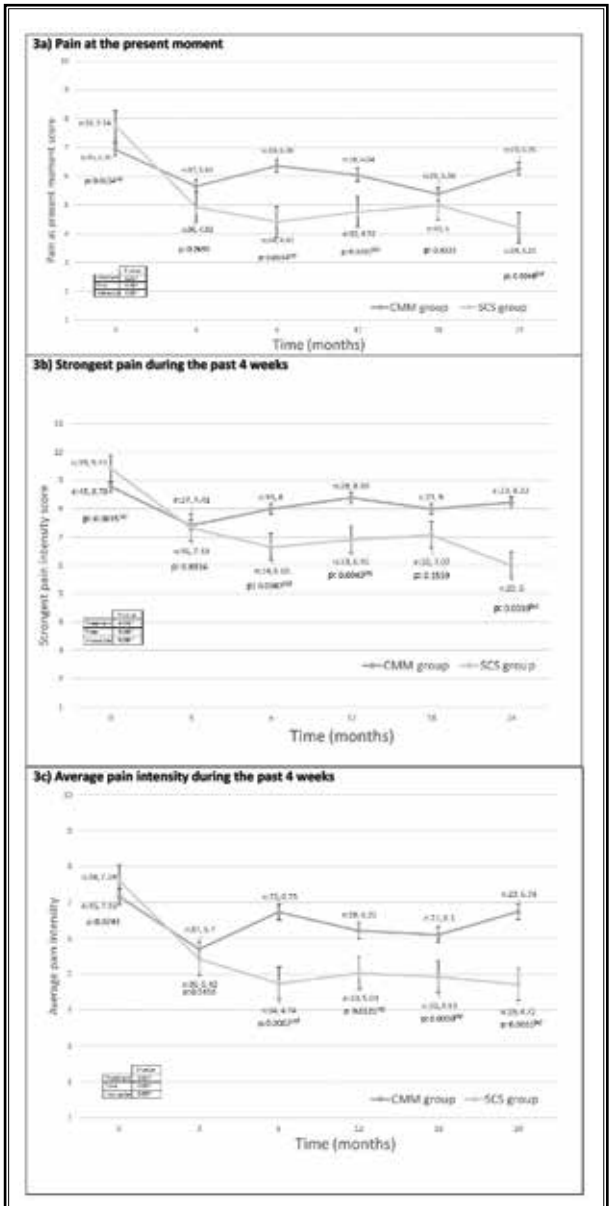

Fig. 3. *Evolution of average scores for pain at present moment, strongest pain during the past 4 weeks, and average pain intensity during the past 4 weeks, for each treatment arm measured through the pain DETECT questionnaire.*
CMM: conventional medical management; SCS: spinal cord stimulation; (a) $P \leq 0.05$.

With a baseline score of 7.74 points, the SCS patients reported statistically significant greater present moment pain at baseline, than the CMM arm patients, with a score of 6.91 ($P = 0.0134$). The SCS patients reported decreasing scores for pain at the present moment in every subsequent programmed visit, reaching statistical significance at months 6 ($P = 0.0014$), 12 ($P = 0.0301$)

and 24 (P = 0.0046). Maximum pain intensity reported during the last 4 weeks also displayed statistically significant differences between the 2 patient groups at baseline: the SCS arm scored 8.78 points versus 9.41 for the CMM arm (P = 0.0015). The SCS patients showed a statistically significant, steady improvement in months 6 (P = 0.0087), 12 (P = 0.0040) and 24 (P = 0.0010). They also reported lower pain intensity on average than the CMM arm for the mentioned visits. There was no statistically significant difference for average pain intensity at baseline, but the SCS arm patients reported greater reductions over time and lower scores than the CMM arm from month 3 up to the last monitoring visit, reaching statistical significance at months 6 (P = 0.0002), 12 (P = 0.0121), 18 (P = 0.0350) and 24 (P = 0.0001). Pain relief was greater than 50% in 13%, greater than 60% in 71% and greater than 70% in 16% in the SCS group. There were no clinically significant differences at 24 months in the CMM group.

Oswestry Disability Index (ODI)

At baseline, the ODI average score was 50.87% for the CMM arm and 59.37% for the SCS arm, with the difference not reaching statistical significance (Table 2). Both arms scores were included within the severe disability range according to the ODI scale. At month 24, the SCS group reported lower functional limitation than the CMM group (43.92% CMM versus 35.4% SCS), with the difference still not reaching statistical significance. The average reduction in ODI score was of 6.47 percentage points (pp) for the CMM arm, in contrast to an average reduction of 23.97 pp reported by the SCS arm patients. The difference for the SCS arm was not only statistically significant (P = 0.0000) but also clinically significant (> 10 pp) (Fig. 2). At the last monitoring visit, the CMM arm reported severe disability state overall, while the SCS patients moved from severe disability at baseline, to moderate disability after 2 years follow-up. CMM patients reported being able to endure pain without painkillers or be fully relieved by them 17.8% at baseline and 13.0% at 24 months (P = 0.7379), although SCS showed 0.0% at baseline and statistical improvements from 3 months (19.4% at 3 months, P = 0.004206; 27.3% at 6 months, P = 0.0004531; 24.2% at 12 months P = 0.00116; 23.3% at 18 months, P = 0.001887; and 21.4% at 24 months, P = 0.003775).

The ODI average score decreased for both treatment arms, with greater reductions for the SCS patients than those on CMM. However, this difference reached statistical significance only at month 6 (P = 0.0368). The CMM patients maintained a severe disability state over the 24-month follow-up, with the exception of the 12-month assessment. Conversely, the SCS patients maintained a moderate disability (range between 35.4% and 39.64%) from month 3 up to the last monitoring visit. There was a significant interaction between group and time, with the SCS group displaying statistically significant greater improvements than the CMM group. The CMM arm showed an irregular trend; the SCS arm reported reduced symptoms from baseline to month 3 and remained relatively stable thereafter.

Regarding pain intensity, 17.77% of the CMM patients reported being able to endure pain without painkillers or be fully relieved by them at baseline. Conversely, neither were reported by any of the SCS patients. At the 24 month follow-up, the percentage of patients who were able to endure pain without painkillers or be fully relieved by them was 13.04% for the CMM arm and 21.43% for the SCS arm. Though this difference was statistically nonsignificant, the increase in the SCS arm from 0% to 21.43% is highly significant (P = 0.003775). Beyond ODI and PainDETECT, no significant differences were found between the 2 groups concerning the basal pharmacological treatment, except for opioids (79% SCS versus 40% CMM, P-value: 0.0004), and no difference was detected at 24 months (opioids 31% SCS versus 25% CMM, P-value: 0.72).

EQ-5D-3L

At baseline, the average EQ-5D-3L utility was 0.32 and 0.22 for the CMM arm and for the SCS arm, respectively (P:NS). At 24 months, the corresponding utility scores were 0.34 and 0.63, respectively (P = 0.0029). Over the month 24, the average utility for the CMM group decreased 0.01 points (n = 23, P = 0.5792), while the SCS group reported a statistically significant increase of 0.39 points (n = 30, P < 0.001). For the EQ-VAS, intra-group differences were significant for both groups: 12.39 for the CMM arm (P = 0.0221) and 24.97 for the SCS arm (P = 0.0001). The EQ-VAS score was 19.17 points higher for the SCS group than for the CMM group at 24 months (P = 0.0081) (Table 2).

Comparative follow-up outcomes indicated that the SCS patients noticed significant improvements, compared to the preceding year, at months 3 (32.43% CMM versus 69.44% SCS, P = 0.0066), 6 (24.4% CMM versus 76.47% SCS, P = 0.0001), and 24 (17.39% CMM versus 80% SCS, P = 0.0000), with a statistically significant time/group interaction effect (P interaction < 0.01). Similar

results were obtained with the EQ-VAS for the same months (22.62% CMM versus 38.58% SCS, *P* = 0.0220; 20.42% CMM versus 45.56% SCS, *P* = 0.0063; 27.13% CMM versus 46.3% SCS, *P* = 0.0081). Here, time and treatment effects were both statistically significant (*P* treatment: 0.03; *P* time: 0.00). The CMM arm followed an irregular time trend over EQ-5D scores, while the SCS arm followed an upward trend over the observed 24 months. For the EQ-VAS, both arms displayed an upward trend, with a greater increase observed in the SCS arm over time for the time horizon considered (Fig. 2).

At month 6, 57.58% of the CMM patients reported none to moderate pain/discomfort, compared to 85.29% of the SCS patients (*P* = 0.0383). At month 24, 4.35% of the CMM patients reported having no problems with usual activities versus 36.67% of the SCS group (*P* = 0.0157); 56.52% CMM patients reported none to moderate pain/discomfort versus 90% within the SCS group (*P* = 0.0086); and 73.91% CMM patients reported none to moderate anxiety/depression versus 96.66% of the SCS patients (*P* = 0.0259).

Medical Outcomes Study Sleep Scale (MOS-SS)

The total MOS-SS 6 dimensions average score was 9.07 points higher for the SCS arm at baseline (P:NS). At 24 months follow-up, both groups of patients showed similar scores (40 CMM versus 40.78 SCS). The SCS group reported a statistically significant reduction in sleep disturbances, with a reduction of 12 points (*P* = 0.0015). Assessment through the MOS-SS 9 dimension scale offered similar results. The SCS patients indicated significantly more problems at baseline, in comparison with the CMM patients (*P* = 0.0398) (Table 2). These differences trace back to the SCS patients reporting feeling drowsy or sleepy during the day (*P* = 0.0173). At 24 months, the MOS-SS 9 dimension score decreased for both groups, but to a larger extent for the SCS arm (P:NS).

Regarding individual items assessment, statistically significant differences were found in the frequency of awakening due to shortness of breath, or with headache at month 6 ("always" for 9.09% of the CMM patients versus 2.94% of the SCS patients, *P* = 0.0091). At month 12, statistically significant differences were observed in napping during the day ("most days" to "always" for 60.71% of the CMM patients versus 18.18 % of the SCS patients, *P* = 0.0132). At 24 months, statistically significant differences were found in average time to fall asleep (34.78% of CMM patients reported needing at least 60 minutes to fall asleep versus 20.69% of the SCS group, *P* = 0.0399), sensation of getting enough sleep (never for 26.09% of the CMM patients versus 0% for the SCS patients, *P* = 0.0350) and frequency of snoring (most days to always for the 45% of the CMM patients versus 44.82% of the SCS patients, *P* = 0.0427).

Hospital Anxiety and Depression Scale (HADS)

The HADS score was high for both treatment types at baseline: 19.39 for the CMM and 21.33 for the SCS arm (P:NS). At month 24, both groups of patients reported lower scores, with the difference still being statistically nonsignificant (8.61 CMM versus 9.72 SCS). At this point, both groups of patients indicated mild problems with anxiety and depression. Regarding intra-group differences, the resulting reduction in this scale was statistically significant for both groups (-10.78 points in the CMM arm, -11.62 points in the SCS arm, *P* < 0.001) (Table 2).

Follow-up total score assessment did not offer statistically significant differences with the exception of the 18-month visit, in which the HADS total average score was higher for the SCS arm (*P* = 0.0387). No significant differences were found for the individual Anxiety Scale throughout the study period for any of the treatment arms. In the individual Depression Scale, the SCS patients scored significantly higher on average than the CMM group at month 18 (*P* = 0.0249).

Discussion

Over the 2-year follow-up period, the SCS patients achieved greater pain relief and HRQoL improvements than the patients who only received CMM. The utility of the SCS patients was 2.86 times higher in comparison with their baseline state according to EQ-5D-3L scale. The SCS patients had stopped reporting clear neuropathic pain components (PD-Q reduction of 10.9 points). Both groups improved significantly in the anxiety and depression PROM, probably due to the tailored and multidisciplinary approach given by the Pain Unit. For most included measures, the SCS group reported more problems at baseline, and comparable or less problems at 24 months. Though the difference in improvement did not reach statistical significance for all measures, the trend across measures indicates that neurostimulation leads to greater symptom alleviation than CMM alone.

Regarding patients symptoms over time, the CMM arm tended to report varying symptoms, while the SCS arm tended to report steady improvements in all

PROMs scales. The proportion reporting pain relief or endurable pain without painkillers dropped to 13.04% in CMM (18% at baseline), and went up to 21.43% for SCS (0% at baseline). Additionally, there was a drop of 42.67% in the proportion of SCS patients reporting "no/little" relief when taking painkillers, indicating that many patients with previously refractory FBSS were achieving treatment effects. Both facts show that the SCS approach decreased pharmacological consumption, compared to CMM, as PROCESS trial (3,27) showed and other studies (12,17,28-30) have suggested. This must not be overlooked given the risks associated with opioid therapy. According to Krames et al (31) study which took into account the use of principles of Safety, Appropriateness, Fiscal Neutrality, and Effectiveness (SAFE principles) in the evaluation of electrical stimulation in FBSS patients, putting off the use of SCS therapy may no longer be justifiable. Authors also suggested that SCS should be considered before submitting a FBSS patient to a long-term systemic opioid approach and repeated spinal surgeries in certain patients may result in more FBSS cases (31).

Our findings are in line with Scalone et al (32) study which also addressed the comparison between CMM and SCS for 24 months in a clinical practice. However, FBSS patients were assessed between 2005 and 2007 and the last 15 years have seen improvements in both the CMM and the SCS approaches. The present study covered more symptoms and health dimensions by using a higher number of FBSS-specific PROMs and specific tools to assess sleep quality and anxiety/depression separately. The mean time after enrollment was higher in the Scalone et al (32) study, (46 days versus 14 days in our study) which comes at a greater risk of bias. Other studies compared both treatment approaches (3,12,29,33,34), but they were based on randomized controlled trials (RCTs) or systematic reviews on RCTs, and included a lower number of PROMs.

In SEFUDOCE-study, patients were representative of FBSS patients profile and their data was indicative of the patient's conditions. In comparison to Kumar (27), our study populations is an older cohort with radicular pain and a large majority of patients with low back pain (97.37%) and radiculopathy (89.61%). Patients also presented worse health state, more years of evolution, and a higher number of previous surgeries. The multicenter approach provides a better basis for generalisation of the findings and the involvement of investigators from different locations offered a wider range of clinical judgements. The prospective cohort study design provides reduced bias risk compared to a retrospective design (35). Furthermore, this study is based on real world data, which offers evidence to support our question about whether clinical trial data matches with clinical practice. In addition, the inclusion of 5 PROMs to evaluate FBSS patients' outcomes, offer a wide analysis and make this study one of the largest in terms of effectiveness measurement.

Limitations

The SCS group had a statistically significant number of younger patients, a tendency towards a higher severity score, and were more frequently treated with opioids than the CMM patients. Patient profiles could be influenced by clinical criteria (i.e., those who are older or have a better pain profile) are less frequently selected for stimulation. This has to be considered when reading the results of the study. Propensity Score matching technique or adding confounders to regression analysis was considered; however, propensity score matching would greatly limit the practical sample size given the unequal symptoms reported by the 2 groups. Inclusion of confounders was also limited by the sample size.

Patients enrolled in the 2 groups had been previously treated according to common practice, but not in a Pain Unit. Although no significant differences were found between the 2 groups concerning the basal pharmacological treatment (except for an increase of opioids for SCS), this should be taken in account in future research.

Furthermore, as CMM or SCS prescription was based on clinical criteria and PROMs, it could be subject to various biases, e.g., selective memory, catastrophism, etc. These limitations should be considered for the interpretation of the results.

Conclusions

This study provides many advantages. First the results are based in several PROMs, the follow-up has a duration of 24 months, and the study relies on routine clinical practice. Essentially, these data help fill the knowledge gap between clinical trials and actual clinical practice with SCS.

The CMM plus SCS approach may provide greater pain relief, greater functional mobility, and improved HRQoL in FBSS patients compared to CMM alone.

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