Review Article

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Non-Invasive Treatments for Failed Back Surgery Syndrome: A Systematic Review

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Abstract

Study design: Systematic Review.

Objectives: The aim of this systematic review is to evaluate the efficacy of non-invasive procedures in relieving chronic pain due to Failed Back Surgery Syndrome (FBSS).

Methods: Since patients who suffered from FBBS are often non-responders to analgesics, we compared Visual Analogical Scale for low back and leg pain, Oswestry Disability Index, trial success rate, adverse events and complications between conservative treatment groups and control groups.

Results: The included studies were 15. Spinal Cord Stimulation (SCS) was performed in 11 trials; 4 studies assessed the efficacy of different epidural injections; one study evaluated repetitive Transcranial Magnetic Stimulation. All the studies reported back and leg pain relief after treatment with SCS, with a significant superiority in high frequences (HFS) group, compared to low frequences (LFS) group. Moreover, disability decreased with each non-invasive treatment evaluated. Epidural injections of steroids and hyaluronidase have shown controversial results. Adverse events were described in 7 studies: lead migration, hardware-related events, infection and incisional pain were the most reported. Finally, trial success rate showed better outcomes for HFS.

Conclusions: Our systematic review highlights the efficacy of conservative treatments in FBSS patients, with an improvement in pain scores and a decrease in disability index, especially after SCS with HFS. However, due to the lack of homogeneity among trials and population characteristics, further studies are needed to confirm the effectiveness of non-invasive interventions in patients affected by FBSS.

Keywords

Failed back surgery syndrome, low back pain, non-invasive treatments, spinal cord stimulation, systematic review

Introduction

Failed Back Surgery Syndrome (FBSS) is defined as a "surgical end-stage after one or several operative interventions on the lumbar neuroaxis, indicated to relieve low back pain (LBP), radicular pain or the combination of both without positive effect.[1] Spine surgery is widely used as a definitive approach to treat chronic low-back pain, especially when

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conservative treatments fail.[2] However, 10-40% of patients experience recurrent or persistent low-back pain with or without leg pain after technically successful spinal surgery.[3,4]Although a clear etiology has not been defined yet, several risk factors have been associated with the development of FBSS including recurrent spine pathology, surgical complications, postoperative inflammation and epidural fibrosis.[5,6] The accumulation of inflammatory mediators may alter nerve sensitive function, leading to chronic neuropathic pain.[7] Moreover, the formation of postoperative scar tissue can result in adhesions to the dura mater and damage nerve roots.[8] First-step therapies are physical therapy and pain medication, although FBSS is often non-responding to analgesic drugs.[9] Further treatments may include interventional procedures, ie steroid injections, percutaneous endoscopic adhesiolysis and neurostimulation before considering re-surgery, which has been shown to be effective only in 5-30% of patients.[10] However, although the availability and continuous development of such different options, a clear consensus about the best therapeutic choice is still missing. The aim of this systematic review is to investigate the efficacy of non-invasive procedures in the management of low chronic pain due to failed back surgery syndrome.

Materials and Methods

Inclusion Criteria

All included studies were randomized clinical trials (RCTs) and observational studies (OS) published in English, that investigated the effectiveness of conservative treatments in patients affected by LBP previously treated with surgical treatment. Conservative treatments included epiduroscopy, epidural injection and Spinal Cord Stimulation (SCS), with high and low frequencies of stimulation. Exclusion criteria were the use of pharmacological treatment, secondary surgical treatment, and studies in which patients underwent multiple non-invasive treatments.

Search Methods

We performed a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines using PubMed–Medline, Scopus, and Google ScholaR.The following search strings were adopted: (((((((("failed back surgery syndrome"[All Fields]) AND ("treatment"[All Fields])) OR (("failed back surgery syndrome"[All Fields]) AND ("management"[All Fields]))) OR (("failed back surgery syndrome"[All Fields]) AND ("neurolysis"[All Fields]))) OR (("failed back surgery syndrome"[All Fields]) AND ("denervation"[All Fields]))) OR (("failed back surgery syndrome"[All Fields]) AND ("nerve ablation"[All Fields]))) OR (("failed back surgery syndrome"[All Fields]) AND ("radiofrequency"[All Fields]))) OR (("failed back surgery syndrome"[All Fields]) AND ("neuromodulation"[All Fields]))) OR (("failed back surgery syndrome"[All Fields]) AND (spinal cord stimulation))) OR (("failed back surgery syndrome"[All Fields]) AND ("steroid injection"[All Fields])). After removing duplicates, two review authors (G.F.P. and S.D.M.) evaluated the abstracts of eligible studies, and any discrepancy was examined with the third reviewer (F.R.). Finally, two reviewers (G.F.P. and S.D.M.) read the full articles to assess the studies for inclusion in this review.

Data Collection, Analysis, and Outcomes

Two independent reviewers (G.F.P. and S.D.M.) conducted data extraction. The following data were extracted: authors, year of publication, study design, level of evidence (LOE), numbers of participants in study and control groups, age and sex of participants, previous surgery and surgical level, duration of pain, type of treatments, follow-up, and results. Visual Analogical Scale (VAS) for low back pain and leg pain, Numeric Rating Scale (NRS) for low back pain and leg pain and Oswestry Disability Index (ODI) were assessed as outcomes in the included studies. The trial success rate was evaluated as patients with a >50% reduction of VAS for back pain. Finally, adverse events and complications were compared between conservative treatment groups and control groups.

Risk of Bias Assessment

The risk of bias of the included RCTs was performed by two reviewers (G.F.P. and S.D.M.) through the Cochrane risk-of-bias tool. That tool classifies seven items as low, unclear, or high risk of bias. Finally, in case of 6-7 items at low risk of bias, the studies reported low risk of bias; for 4-5 items at low risk of bias, the studies reported unclear risk of bias; for <4 items at low risk of bias, the studies reported high risk of bias.

Results

Results of the Search

The literature search produced 1070 articles. After removal of duplicates, 1009 articles were screened for title and abstract, leading to 40 eligible papers, which were read in full-text. Then, 24 studies were refused for the following motivations: not reporting selected outcomes (n = 10), non-specific design of the study (n = 5), non-conventional conservative treatment used (n = 4), same population with lower follow-up (n = 4), protocols of RCT (n = 2) Finally, 15 studies were included in the systematic review (Figure 1).

Characteristics of the Included Studies

The studies were 13 RCTs and 2 observational studies (Table 1). The overall number of patients in the included studies is 1063. The duration of pain was reported in 11 studies and ranged from 7.6 to 192 months. Patients' mean age ranged

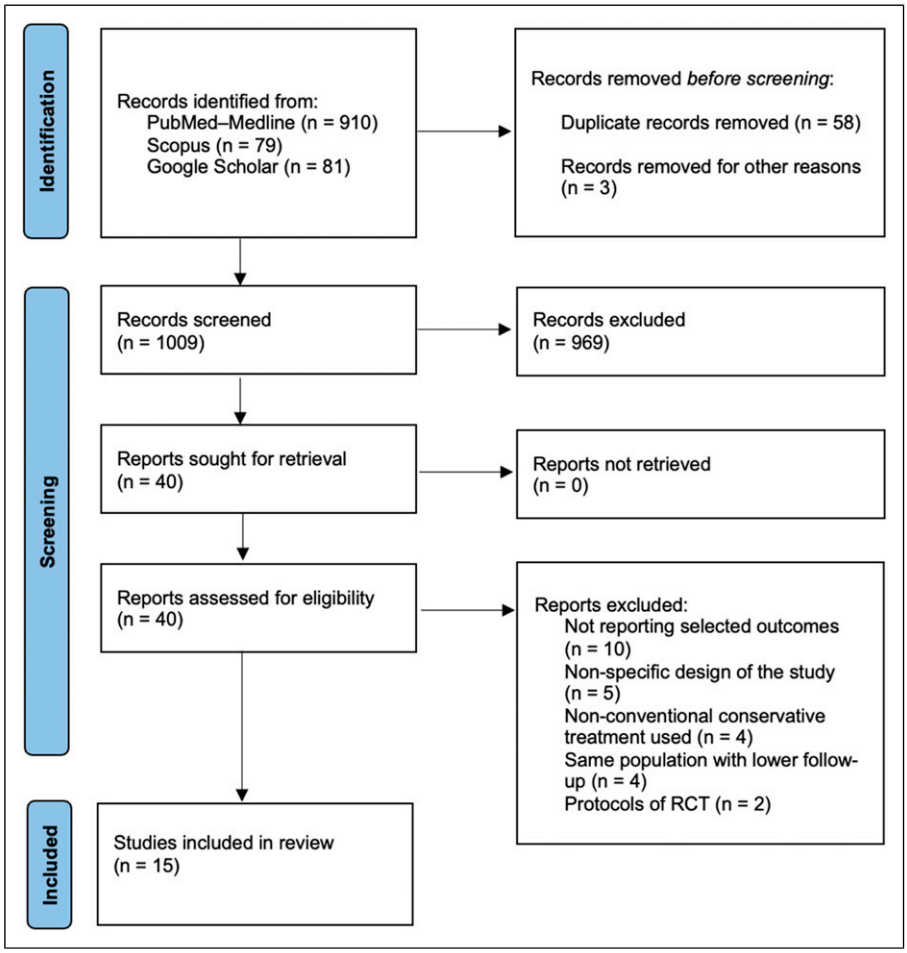

Figure 1. Preferred reporting items for systematic review and meta-analysis (PRISMA) flow diagram.

from 45.9 to 62.1 years old. The male percentage ranged from 30 to 68% among the studies, with an almost equal distribution between genders. SCS was performed in 10 studies; in 4 studies it was compared at high frequences (HFS) vs low frequences (LFS); in 2 studies was evaluated burst stimulation; in 3 studies SCS was compared with usual care; in one study SCS was implemented with Peripheral Nerve Field Stimulation (PNFS). A total of 4 studies assessed the efficacy of various types of epidural steroid injections (ESI). Finally, one study evaluated the beneficial effects of repetitive Transcranial Magnetic stimulation (r-TMS). The mean follow-up was 13.3 months, ranging from 1 to 36 months. The detailed treatment groups are described in Table 2.

Clinical Outcome Data

Back pain was assessed by VAS in 9 studies, NRS in 3 studies,[11-13] and EuroQol VAS (EQ-VAS) in one study.[14] All the studies reported bak pain relief after the treatment in both groups. A significant improved in back pain symptoms was observed in HFS groups compared to LFS groups; [15-17]while one study demonstrated significant superiority of burst stimulation over HFS in bak pain relief.[18] Leg pain was evaluated in 7 studies; the used score was VAS, unless one study,[19] which adopted the Douleur Neuropathique en 4 Questions (DN4). HFS produced significant improvement in leg pain compared to LFS in 3 studies.[15-17] Disability was assessed in 10 studies through ODI score. In all the groups of the included studies it has been shown an improvement of ODI. However, when analyzing SCS, only the study by Kapural et al[17] demonstrated statistically significant benefit for HFS group compared to LFS ($P = .02$). The occurrence of adverse events was described in 7 studies. The most common is represented by lead migration. Other complications involved other hardware-related events, infections and incisional pain. The trial success rate was evaluated in 5 studies, showing better outcomes for HFS compared to LFS (Table 3).

Methodological Evaluation

Among the 13 RCTs, the Cochrane risk-of-bias tool reported 5 studies (38%) at low risk of bias, 7 studies (54%) at moderate risk of bias, and only one study (8%) at high risk of bias (Table 4).

Table 1. Main characteristics of the included studies.

Author (year)	Study design	LOE	Duration of pain	Treatment (group I)	N	Age	Sex (%M/%F)	Treatment (group II)	N	Age	Sex (%M/%F)
Manchikanti et al (2009)[11]	RCT	I	192 m	Caudal ESI with catheterization up to S3	60	52 y	42%/58%	Percutaneous Adhesiolysis	60	52 y	42%/58%
Manchikanti et al (2010)[12]	RCT	I	156 m	Caudal Epidural Injection	70	52.4 y	39%/61%	Caudal ESI	70	48 y	51%/49%
Rahimzadeh et al (2014)[33]	RCT	I	7.6 m	TFESI + Hyaluronidase	12	45.9 y	58%/42%	TESI	13	48 y	54%/46%
Rapčan et al (2018)[34]	RCT	I	N.R.	Mechanical Adhesiolysis	22	54 y	55%/45%	Adhesiolysis with Corticosteroid and Hyaluronidase	23	46.5 y	48%/52%
Bursali et al (2021)[19]	RCT	I	1-10 y (55%), >10 y (40%)	r-TMS	10	48.2 y	30%/70%	Sham r-TMS	10	54.4 y	30%/70%
North et al (2019)[35]	RCT	I	10.5 y	SCS HFS	50	59.4 y	46%/54%	SCS LFS	49	59 y	55%/45%
Bolash et al (2019)[15]	RCT	I	10.6 y	SCS HFS	38	58.5 y	47%/53%	SCS LFS	34	58.2 y	58%/42%
van Gorp et al (2018)[36]	RCT	I	N.R.	PNFS - SCS	28	46.5 y	68%/32%	SCS	24	53.5 y	54%/46%
Al-Kaisy et al (2018)[16]	RCT	I	5.1 y	SCS	24 *	47.9 y *	66.7%/33.3% *	Sham SCS	24 *	47.9 y *	66.7%/33.3% *
Pèrez et al (2021)[14]	OS	II	8 y	SCS	39	53 y	46.2%/53.8%	CMM	46	60.7 y	19.6%/80.4%
Eldabe et al (2018)[37]	RCT	I	13.3 y	SQS + OMM	56	50.9 y	42.9%/57.1%	OMM	60	52.2 y	43.3%/56.7%
Kapural et al (2015)[17]	RCT	I	13.6 y	HFS	92	54.6 y	38%/62%	LFS	87	55.2 y	41.4%/58.6%
Muhammad et al (2017)[18]	OS	II	3.2 y	Burst stimulation	8	62.1 y	44%/56% *	SCS	8	56 y	44%/56% *
De Andres et al (2017)[13]	RCT	I	N.R.	HFS	26	51.6 y	57.7%/42.3%	LFS	29	53.8 y	37.9%/62.1%
van Haven bergh et al (2014)[38]	RCT	I	N.R.	Burst stimulation 500 Hz	15 *	52 y *	53%/47%*	Burst stimulation 1000 Hz	15 *	52 y *	53%/47% *

LOE: Level Of Evidence; N: number of participants; m: months; y: years; RCT: Randomized Controlled Trial; OS: Observational Study; N.R.: not reported; ESI: Epidural Steroid Injection; TFESI: Transforaminal ESI; r-TMS: repetitive Transcranial Magnetic stimulation; SCS: Spinal Cord Stimulation; HFS: High Frequency Stimulation; LFS: Low Frequency Stimulation; PNFS: Peripheral Nerve Field Stimulation; CMM: Conventional Medical Management; SQS: subcutaneous nerve stimulation; OMM: optimized medical management.
*value for both groups.

Discussion

Pain management in FBSS remains a challenge and only a few studies have been performed to investigate the efficacy of conservative treatments for chronic low-back pain and leg pain. These patients are often non-responders to analgesics, and non-invasive approaches such as epiduroscopy, epidural injection and Spinal Cord Stimulation may be effective therapeutic choices, as alternatives to spine surgery. The role of epidural injections of steroids and hyaluronidase in FBSS is still controverted, due to a paucity of literature. Injections in the epidural space in back and leg pain have shown controversial results so far.[20-23] Moreover, the effectiveness of hyaluronidase in producing pain relief in FBSS and spinal

Table 2. Clinical Results of the Included Studies.

Author (year)	Type of treatment (group I)	Type of treatment (group II)	Follow-up	Result
Manchikanti (2009)	Epidurogram followed by passage of a Racz catheter up to S3 followed by injection of 5 mL of 2% preservative-free lidocaine; and injection of 6 mL of .9% sodium chloride solution, 6 mg of non-particulate Betamethasone and 1 mL of sodium chloride solution	Adhesiolysis and placement of Racz catheter with injection of 5 mL of 2% preservative-free lidocaine, 6 mL of 10% sodium chloride solution and 6 mg of non-particulate Betamethasone and 1 mL of sodium chloride solution	12 months	Significant pain relief and functional status improvement was recorded in 73% of patients in Group II vs 12% in Group I ($P < .001$).
Manchikanti (2010)	Caudal epidural injections of local anesthetic (lidocaine .5%)	Caudal epidural injections with .5% lidocaine 9 mL mixed with 1 mL of 6 mg non-particulate Celestone	12 months	Combined pain relief and disability reduction was recorded in 53% of the patients in the local anesthetic group and 59% of patients in the local anesthetic and steroidgroup, with no significant differences noted with or without steroid over a period of 1-year.
Rahimzadeh (2014)	TFESI wit Bupivacaine 5 mg (1 mL) + Triamcinolone 40 mg (1 mL) + Saline solution 10% (2 mL) + Hyaluronidase 1.500 IU reconstituted in 1 mL distilled water (HYL)	TFESI with Bupivacaine 5 mg (1 mL) + Triamcinolone 40 mg (1 mL) + Saline solution 10% (2 mL) + 1 mL distilled water (NSL)	1 month	The addition of hyaluronidase has a positive impact on minimizing the pain scores, better for the herniation discopaty than spinal stenosis ($P < .001$).
Rapčan (2018)	Injection of 5 mL of .5% bupivacaine (supplemented up to 20 mL with saline) and mechanical lysis of the epidural fibrotic by laser (4), radiofrequency (15), or the balloon technique (3)	Mechanical lysis of the epidural fibrotic by laser (5), radiofrequency (16), or the balloon technique (4) plus a solution of hyaluronidase and injectable corticosteroid methylprednisolone acetate 80mg into the place of conflict	12 months	A significant improvement was recorded in ODI in both groups after 6 months ($P < .05$). An improvement of leg and back pain was found in both groups after 6 months.
Bursali (2021)	5 Hz of r-TMS as a 20-minute (1000 pulses) daily session, 5 days per week, for a total of 10 sessions	Sham r-TMS with the same protocol	3 months	Significant improvements were achieved in DN4, ODI, BDI, and PSQI scores in the r-TMS group in comparison to the sham group.
North (2019)	SCS: 10 kHz at a pulse width of 30 μsec	SCS: 50 to 1500 Hz with pulse widths between 30 and 1000 μsec	1 month	The overall trial success rate was 92% for HFS and 84% for LFS.
Bolash (2019)	SCS: 10 kHz and 30 μsec	SCS: 10– 1500 Hz and 50-500 μsec	6 months	At follow-up, the mean back and leg pain VAS reduction was 77% for the HF arm and 64% for for the HF arm.
van Gorp (2018)	SCS combined with PNFS for a period of three months with a bipolar configuration, stimulation frequency set at a rate of 30 Hz, while amplitude and pulse width were individually adjusted	SCS and inactive PNFS-leads	12 months	At 12-month follow-up, PNFS in addition to SCS continues to provide a statistically significant and clinically relevant relief of low back pain in FBSS patients in whom SCS alone is effective for relief of leg pain only ($P < .01$).
Al-Kaisy (2018)	SCSt at Various Kilohertz Frequencies: 1200 Hz at 180 μsec, 3030 Hz at 60 μsec, and 5882 Hz at 30 μsec	Sham SCS with the generator turned on and discharging, but without electricity transmitted to the lead	12 months	5882 Hz stimulation produces significant pain relief for low back pain compared with lower frequencies and sham stimulation ($P = .002$).

(continued)

Table 2. (continued)

Author (year)	Type of treatment (group I)	Type of treatment (group II)	Follow-up	Result
Pèrez et al (2021)	83% conventional SCS (Tonic stimulation: 40-70 Hz; 280-420 microsec; 3.8-6 mA) and 17% high-frequency SCS (1000 Hz; 200 microsec; 2 mA)	Pharmacological treatment, physical therapy, nerve block and trigger point block, epiduroscopy, radiofrequency and epidural procedures	24 months	SCS may improve the HRQoL and functionality of FBSS patients with refractory pain in the long-term compared to CMM alone ($P < .05$).
Eldabe (2018)	Placement of a neurostimulator and up to two subcutaneous percutaneous cylindrical leads in the area of pain	Optimized medical management	36 months	A total of 33.9% of subjects in the SQS + OMM arm and 1.7% in the OMM arm presented a >50% reduction in back pain intensity at month 9 ($P < .0001$).
Kapural (2015)	SCS: 10 000 Hz, 30 μsec stimulation with amplitude and stimulation location adjusted	SCS: Low-frequency (40-60 Hz), longer duration (300-600 msec), and higher amplitude (4-9 mA) pulses	24 months	The responder's rate to HF10 therapy was statistically superior to traditional SCS for back pain and leg pain (respectively $P < .001$ and $P = .003$).
Muhammad (2017)	Burst rate of 40 Hz, an intraburst rate of 500 Hz, a pulse width of 1000 ms, and average amplitude of 2.36 mA	Ten kilohertz SCS was set to a pulse width of 30 microsec and average amplitude of 2.88 mA	20 months	Burst and 10 kHz are effective in reducing LBP intensity with a percentage change from baseline of 87.5% for burst and 54.9% for 10 kHz SCS. At follow-up, LBP intensity was not statistically different for burst compared with 10 kHz ($P = .13$).
De Andres et al (2017)	SCS at frequency 2 Hz to 10.000 Hz; pulse width 20 μs to 1 ms; amplitude 0 mA to 15 mA	SCS at amplitude, 3-10 mA; frequency, 10-40 Hz; and pulse width, 60-450 ms	12 months	Changes in scores did not differ based on high vs conventional frequency, with significant global average reduction at one year similarly for both groups.
van Haven bergh (2014)	Burst Stimulation at 500 Hz with 1000-μsec pulse width 40 times per second	Burst Stimulation with five spikes at 1000 Hz with 500-μsec pulse width 40 times a second	N.R.	No significant difference between 500 Hz burst mode and 1000 Hz burst mode were observed for back pain ($P = .90$), limb pain ($P = .76$), or general pain ($P = .55$).

ESI: Epidural Steroid Injection; TFESI: Transforaminal Epidural Steroid Injection; r-TMS: repetitive Transcranial Magnetic stimulation; SCS: Spinal Cord Stimulation; HFS: High Frequency Stimulation; LFS: Low Frequency Stimulation; CMM: Conventional Medical Management; SQS: subcutaneous nerve stimulation; OMM: optimized medical management; LBP: Low Back Pain; N.R.: not reported.

stenosis is largely unknown. Epidural scar tissue could be disrupted by hyaluronidase, a lysing enzyme that is supposed to enlarge the spread of other injected drugs, such as corticosteroids, reducing fibrosis in the epidural space during epiduroscopy. Few trials have studied the effects of injections in epidural space. Devulder et al[24] and Yousef et al[25] demonstrated that hyaluronidase administration improved pain scores. In a study by Schulze et al,[26] corticosteroids and hyaluronidase targeted injection induced a reduction of back pain and inflammation, with a resulting epidural neuroplasty. Heavner et al[27] compared the use of epidural saline plus hyaluronidase to saline alone and they did not show significant differences in clinical outcome. Recent trials have showed that addition of hypertonic saline to the solution in patients with FBSS improves short term pain control,[25,28] probably due to its osmotic and anti-edema action nearby nerve roots. Another non-invasive treatment for chronic pain in FBSS patients is Spinal Cord Stimulation. SCS consists of electrical stimulation of the dorsal columns of the spinal cord, using a high frequency of stimulation of 10 kHz (HFS) or a lower frequency of 1500 Hz or less (LFS). Some systematic reviews and meta-analyses concluded that SCS decreases analgesics consumption, reduces pain, and improves quality of life while being also cost-effective.[29-31] Compared to the past, SCS systems have been implemented with more options and components, so the debate is now on efficacy, cost-utility, adverse events, and indications. The predominant indication continues to remain stable for neuropathic pain from FBSS.

Table 3. Clinical Outcomes.

Author (year)	Groups	N	Back pain		Leg pain		ODI		Adverse events and complications (N)	Trial success rate (%)
			pre	post	pre	post	pre	post		
Manchikanti (2009)	Group I (ESI)	60	7.9 ± .8	6.1 ± 1.4	N.R.	N.R.	28.6 ± 4.1	23.3 ± 5.8	0	N.R.
	Group II (PA)	60	8.1 ± .8	4.0 ± 1.2	N.R.	N.R.	31.2 ± 4.1	15.8 ± 5.6	0	N.R.
Manchikanti (2010)	Group I (Epidural Injection)	70	7.9 ± 1.0	4.5 ± 1.9	N.R.	N.R.	30.5 ± 4.6	17.8 ± 7.1	0	N.R.
	Group II (ESI)	70	7.8 ± .9	4.2 ± 1.7	N.R.	N.R.	29.1 ± 4.5	16.5 ± 7.0	0	N.R.
Rahimzadeh (2014)	Group I (TFESI + Hyaluronidase)	12	3.1 ± 2.0	1.5 ± 2.2	N.R.	N.R.	N.R.	N.R.	0	N.R.
	Group II (TFESI)	13	3.4 ± 1.5	2.5 ± 2.2	N.R.	N.R.	N.R.	N.R.	0	N.R.
Rapčan (2018)	Group I (Mechanical Adhesiolysis)	22	7 ± 1.64	7 ± 1.63	6 ± 1.72	6 ± 1.54	65 ± 15.57	54 ± 17.78	N.R.	N.R.
	Group II (Adhesiolysis with Corticosteroid and Hyaluronidase)	23	8 ± 2.19	6 ± 2.33	7 ± 1.54	6 ± 2.11	58 ± 18.46	48 ± 19.14	N.R.	N.R.
Bursali (2021)	Group I (r-TMS)	10	6.3 ± 2.83	3.3 ± 2.91	6.5 ± 1.65	4.2 ± 1.93	35.0 ± 3.37	23.2 ± 8.72	Mild headache (1)	N.R.
	Group II (sham r-TMS)	10	5.9 ± 3.6	5.0 ± 3.2	5.4 ± 1.78	6.2 ± 2.3	30.1 ± 6.26	28.1 ± 5.97	0	N.R.
North (2019)	Group I (HFS)	50	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	Electrode migration (3), Other (3)	92
	Group II (LFS)	49	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	Infection (1), Electrode migration (7), Unintended stimulation (5), Incisional pain (3), Loss of stimulation (2), Other (2)	84
Bolash (2019)	Group I (HFS)	38	75.8 ± 13.1	17.8 ± 14.1	55.1 ± 27.2	13.3 ± 14.1	53	30	Electrode migration (5), Loss of stimulation (1), Incisional pain (2), Other (4)	92
	Group II (LFS)	34	77.5 ± 9.9	27.8 ± 23.2	61.5 ± 24.1	22.3 ± 24.4	55	32	Infection (1), Electrode migration (10), Loss of stimulation (4), Unintended stimulation (3), Lead breakage (2), Incisional pain (5)	84
van Gorp (2018)	Group I (PNFS - SCS)	28	72.3 ± 11	41.6 ± 25.9	70.4 ± 12.6	29.7 ± 23.2	60	43	Hardware related events (16), Infection (5), Pain (10), Other (4), Acute lumbar disc herniation (1), Death (1)	N.R.
	Group II (SCS)	24	73.9 ± 9.3	48.2 ± 26.3	71.8 ± 11.7	24.4 ± 23	58	46		
Al-Kaisy (2018)	Group I (SCS 5882 Hz)	24	7.75 ± 1.13	3.22 ± 1.98	3.06 ± 2.55	1.81	N.R.	N.R.	Pain at the implanted pulse generator site (3), Minor lead migrations (3), Other (2)	N.R.
	Group II (SCS 3030 Hz)			4.57 ± 2.09		2.2	N.R.	N.R.		N.R.
	Group III (SCS 1200 Hz)			4.51 ± 1.87		2.37	N.R.	N.R.		N.R.
	Group IV (sham SCS)			4.83 ± 2.45		2.51	N.R.	N.R.		N.R.
Pèrez (2021)	Group I (SCS)	31	21.36 *	46.3	N.R.	N.R.	59.4	35.4	N.R.	69
	Group II (CMM)	23	17.52 *	27.13	N.R.	N.R.	50.9	43.9	N.R.	32
Eldabe (2018)	Group I (SQS + OMM)	56	68.8 ± 13.4	36.9 ± 24	7.2 ± 8.2	8.4 ± 11.8	52.8 ± 12.1	40.7 ± 15.2	178: Other (67.2%), Medication (18.3%), Biological-related (7.5%), Hardware-related (2.7%), Therapy-related (2.2%)	34
	Group II (OMM)	60	70.1 ± 14.0	67.5 ± 18.1	4.6 ± 7.7	8.1 ± 17.6	47.0 ± 11.5	46.7 ± 12.3		2
Kapural (2015)	Group I (HFS)	85	7.4 ± 1.3	2.4 ± 2.3	7.1 ± 1.5	2.4 ± 2.5	69.4	30.6	Wound complications (5), Paresis (1)	76
	Group II (LFS)	71	7.8 ± 1.2	4.5 ± 2.9	7.6 ± 1.4	3.9 ± 2.8	77.5	42.3	Wound complications (3), Extradural abscess (1), Other (4)	49
Muhammad (2017)	Group II (Burst stimulation)	8	8 ± .76	1 ± 1.41	N.R.	N.R.	N.R.	N.R.	0	N.R.
	Group II (HFS)	6	8 ± .63	3.5 ± 3.27	N.R.	N.R.	N.R.	N.R.	0	N.R.
De Andres (2017)	Group I (HFS)	26	7.69 ± 1.17	6.06 ± 2.41	N.R.	N.R.	27 ± 5.18	23 ± 7.06	Lead migration (5), Other (3)	N.R.
	Group II (LFS)	29	7.6 ± 1.06	5.86 ± 2.46	N.R.	N.R.	27.2 ± 5.21	22.1 ± 7.86	Lead migration (2), Other (2)	N.R.

ESI: Epidural Steroid Injection; PA: Percutaneous Adhesiolysis; TFESI: Transforaminal ESI; r-TMS: repetitive Transcranial Magnetic stimulation; SCS: Spinal Cord Stimulation; HFS: High Frequency Stimulation; LFS: Low Frequency Stimulation; CMM: Conventional Medical Management; SQS: subcutaneous nerve stimulation; OMM: optimized medical management.

*EQ-VAS: values between 100 (best imaginable health) and 0 (worst imaginable health).

Table 4. Cochrane Risk-of-Bias Tool for Randomized Controlled Trials.

Study	Random sequence generation	Allocation concealment	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Selective reporting	Other sources of bias	Risk of bias
Manchikanti (2009)	L	L	U	L	L	L	U	U
Manchikanti (2010)	L	L	L	L	L	U	L	L
Rahimzadeh	L	L	L	L	L	U	U	U
Rapcan	L	L	L	L	L	L	U	L
Bursali	L	L	L	L	L	U	L	L
North	L	L	U	U	H	L	U	H
Bolash	L	L	H	H	L	L	U	U
Van Gorp	L	L	H	L	L	L	L	L
Al-Kaisi	L	L	L	U	L	U	U	U
Edalbe	L	L	H	U	L	L	U	U
Kapural	L	L	H	H	L	L	U	U
De Andres	L	L	L	L	L	U	L	L
Van Haven bergh	L	L	L	L	H	L	U	U

L: low; U: unclear; H: high.

The National Institute for Health and Care Excellence (NICE) in the UK recommends SCS as a treatment for patients suffering from refractory chronic neuropathic pain conditions, including chronic low back pain. In a systematic review and meta-regression analysis,[32] SCS is described as an effective pain-relieving treatment for FBSS in those with predominant leg pain, independently of a prior history of back surgery. However, this study included almost exclusively case series, therefore RCTs are needed to confirm the effectiveness of SCS in the chronic low back pain population with predominant low back pain. The evidence for SCS in the treatment of neuropathic pain is continuing to grow as more prospective and randomized trials are being performed. In all the included studies, the performed procedures have determined clinically relevant pain relief for LBP and leg pain. Moreover, it has been shown a statistically significant decrease in LBP and leg pain in FBSS patients treated with SCS HF, compared with SCS LF or sham stimulation. It has been demonstrated an improvement in ODI in all the treated groups. However, there were no significant differences among the various study groups. Finally, no adverse events or complications occurred in the patients who underwent ESI, while only a low percentage of patients treated with SCS reported complications. Furthermore, among the complications, most were represented by electrode migration or pain. Therefore, it can be stated that these are safe and easily practicable treatments. The most important limitation of this research is determined by the lack of homogeneity among the included studies, which did not allow us to carry out a meta-analysis among the LOE I studies. The literature search produced studies that mainly investigated two procedures (ESI and SCS), but with different comparisons among the groups. In fact, the patients underwent several different interventions in the included trials, with great heterogeneity of type and duration of the treatments. Moreover, population characteristics could not be guaranteed to be the same in all the studies.

Conclusion

Our systematic review highlights the efficacy of conservative treatments in FBSS patients, with an improvement in pain scores and a decrease in disability index, especially after SCS with HFS, while the role of epidural injections of steroids and hyaluronidase is still controversial. Many therapeutic options could be evaluated as possible alternatives to spine surgery, yet the etiology of the syndrome is still not cleaR.There's an open debate about efficacy, adverse events, indications and cost-effectiveness, therefore further studies may implement our knowledge and demonstrate the superiority of a particular treatment over the others.

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