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Spinal Cord Stimulation in Peripheral Arterial Disease: A 10-Year Systematic Review of Pain Relief and Limb Salvage Outcomes

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ABSTRACT

This systematic review evaluated the efficacy and safety of Spinal Cord Stimulation (SCS) in patients with Peripheral Arterial Disease (PAD). The study analysed pain relief and limb salvage outcomes by systematically reviewing relevant literature published in the past ten years. Out of 191 records screened, a total of 10 studies were included, involving 1,079 patients. The selected studies used various research designs and assessed either pain levels or limb salvage, or both. Pain levels were mainly measured using Visual Analog Scale (VAS) scores at different follow-up intervals, showing significant pain relief over time. Limb salvage outcomes were described as limb survival rates or the percentage of patients requiring amputations, with positive results observed over time. The review acknowledges limitations, such as challenges encountered during the bias assessment and time constraints. Overall, the findings support the efficacy and safety of SCS and suggest its potential as a first-line treatment for conditions like critical limb ischemia (CLI), peripheral arterial disease (PAD), and peripheral vascular disease (PVD). It is recommended for future studies to use a single method for assessing pain levels, such as the Visual Analog Scale (VAS), and implement a standardized test to assess limb salvage as well, which ensures homogeneity of data and enables future meta-analysis. Eventually, it would be encouraged for future research and health professionals to employ artificial intelligence tools to anticipate the effectiveness of SCS for each patient individually before the condition deteriorates to the point where limb amputation becomes necessary.

Keywords: Spinal Cord Stimulation (SCS); Peripheral Arterial Disease (PAD); Peripheral Vascular Disease (PVD); Pain Relief; Limb Salvage; Critical Limb Ischemia (CLI); Neuromodulation; Spinal Cord Stimulators; High-Frequency Stimulation (HFS); Conventional Stimulation

Abbreviations: SCS: Spinal Cord Stimulation; PAD: Peripheral Arterial Disease; PVD: Peripheral Vascular Disease; VAS: Visual Analog Scale; CLI: Critical Limb Ischemia; HFS: High-Frequency Stimulation

Introduction

Spinal cord stimulators are implantable devices made up of thin wires and a battery pack, positioned between the spinal cord and vertebrae (the epidural space) [1]. Spinal cord stimulation, also known as neuromodulation, is a pain treatment or procedure that uses a relatively small amount of electrical current to activate specific nerve fibers in the spinal cord [2]. That current, in effect, blocks pain signals before they reach the brain [3]. Pain is caused by several pain systems, which are composed of integrative neuronal groups that send excitatory or inhibitory signals to nociceptors. These signals are delivered to second-order neurons in the spinal cord, primarily in the region of the dorsal horn (central pathways), which then transfer them to the brainstem (integrative neurons) via projection neurons [4]. The spinal cord stimulator employs pulsed electrical currents near the spinal cord for the sake of pain management; neuromodulation now entails the placement of leads in epidural space, where electrical pulses are delivered to the spinal cord via a small device similar to a pacemaker. It aids in the management of chronic pain and the reduction of the use of opioid drugs [5]. SCS technology is classified into two types including, conventional stimulation and high-frequency stimulation (HFS).

Conventional stimulation stimulates the spinal cord using low-frequency electrical pulses (usually in the range of 40-60 Hz), which is inserted into the buttock or abdomen beneath the skin, where the leads are positioned along the spinal cord, whereas HFS uses high-frequency pulses (about 10 kHz) to engage a distinct set of neurons. HFS has been demonstrated to be more effective at relieving pain [6] and having fewer negative effects than traditional stimulation. Boston Scientific [7-11] are the big leaders in manufacturing SCS devices, with different features and capabilities like rechargeable and non-rechargeable batteries, wireless and wired programming. Boston Scientific offers a lot of SCS devices such as Precision Spectra, Precision Plus, Spectra WaveWriter, WaveWriter Alpha, Precision Montage MRI, and Precision Novi [7], Medtronic also offers multiple devices such as Intellis, Vanta, and Primeadvanced Surescan MRI [8], Abbott offers The Proclaim [9], Nevro offers Senza [10], and Curonix offers Freedom [11], all these devices offer different features some of which include producing multiple waveforms simultaneously, the ability to have an MRI while having the device implanted at the same time, stimulating different kinds of waveforms, and providing HFS and conventional stimulation in the same device.

The gate control theory suggests a mechanism located in the Substantia gelatinosa of the spinal cord's dorsal horn, this mechanism is called the gate, it regulates the transmission of pain signals to the brain, if the gate is open, the pain signals are transmitted to the brain, resulting in the perception of pain, if the gate is closed, pain signals are blocked, preventing the sensation of pain [12-16]. The theory considers two types of fibers, large-diameter non-nociceptive, transmitting touch, pressure, vibration, and small-diameter nociceptive, transmitting pain, which carry information from the site of injury to transmission cells that carry the pain signal up to the brain, and to the Inhibitory Interneurons that impede transmission cell activity. The balance of activity between these fibers can either open or close the gate and thus control the sensation of pain [13,14]. Pain can be managed by manipulating the gate mechanism to reduce pain perception [12]. Non-noxious stimuli like touch, pressure and vibration can close the gate and interfere with pain signals [12,13,15]. Techniques such as Transcutaneous Electrical Nerve Stimulation (TENS) [12,13] and Interferential Current (IFC) therapy [12] stimulate specific nerve fibers to close the gate [12,13]. Mindfulness based pain management (MBPM) states that the brain controls the perception of pain and can be trained to ignore certain types of pain that are not useful [13].

Emotions and activities that stimulate large nerve fibers like exercise, and strategies like distraction, relaxation techniques, optimism, and thought stopping can also help close the gate and relief the pain [12-16]. Peripheral Arterial Disease (PAD) occurs due to narrowing or blocking in the arteries from plaque build-up, it causes a reduction or a blockage in the blood flow to the limbs which results in pain, soreness, cramps, numbness and in critical conditions cutting off the limb, PVD (Peripheral Vascular Disease) describes any disorder affecting the blood vessels outside of the heart and brain, including PAD. Additionally, a complete blockage of blood flow to the leg results in a more severe type of PAD known as Critical limb ischemia (CLI), if left untreated, this can cause destruction of tissue and possibly amputation. The common ways that are used to treat PAD are using medications that improve blood flow and sometimes surgeries are needed, these treatments might not be very efficient or might be costly.

Materials and Methods

Eligibility Criteria

This systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, The inclusion criteria required studies to be published in the past ten years (May-2013 to May-2023). The studies must use SCS treatment for PAD, PVD, or CLI, and specifically examine at least one of the outcomes of interest, pain levels and limb salvage. On the other hand, studies that used treatments other than SCS that affect the outcomes, and those that score low in the NOS bias test have been excluded.

Information Sources

Five databases were covered. Originally, there were six databases, but due to access issues with EMBASE, it was decided to remove it. Consequently, the databases consist of PubMed, Scispace, Elicit, Google Scholar, and the Cochrane Library. The last search across all the databases was conducted on May 2, 2023.

Search Strategy

On PubMed and Cochrane Library, the MeSH search strategy was used on combinations of the terms SCS, PAD, pain measurement, limb salvage, and their synonyms (**Appendix Text**); the term PAD was also swapped with PVD and CLI to ensure all relevant studies were covered. For the other databases, the keywords "spinal cord stimulation, peripheral arterial disease" were used, along with swapping PAD with PVD and CLI, a filter was applied to show studies published within the last 10 years.

Selection Process

Sixty-six studies were skimmed from PubMed, 42 from Google Scholar, 18 from the Cochrane Library, 34 from SciSpace and 37 from Elicit, all have been evaluated for their relevance to the research topic. After the initial screening, 33 studies satisfied the inclusion criteria. To obtain the full-text reports of those studies, multiple online sources including the Chrome extension Unpaywall were utilized. After extracting and categorizing the data, 12 narrative reviews, 4 case reports, 6 systematic reviews, and 1 comprehensive literature search were excluded due to high probability of bias, limited number of cases, overlap of data from systematic reviews, and outdated reviewed studies older than 10 years. In the end, ten studies complied with the specified criteria as demonstrated in (Figure 1) after performing a detailed examination with the help of the data extraction table. (Table 1).

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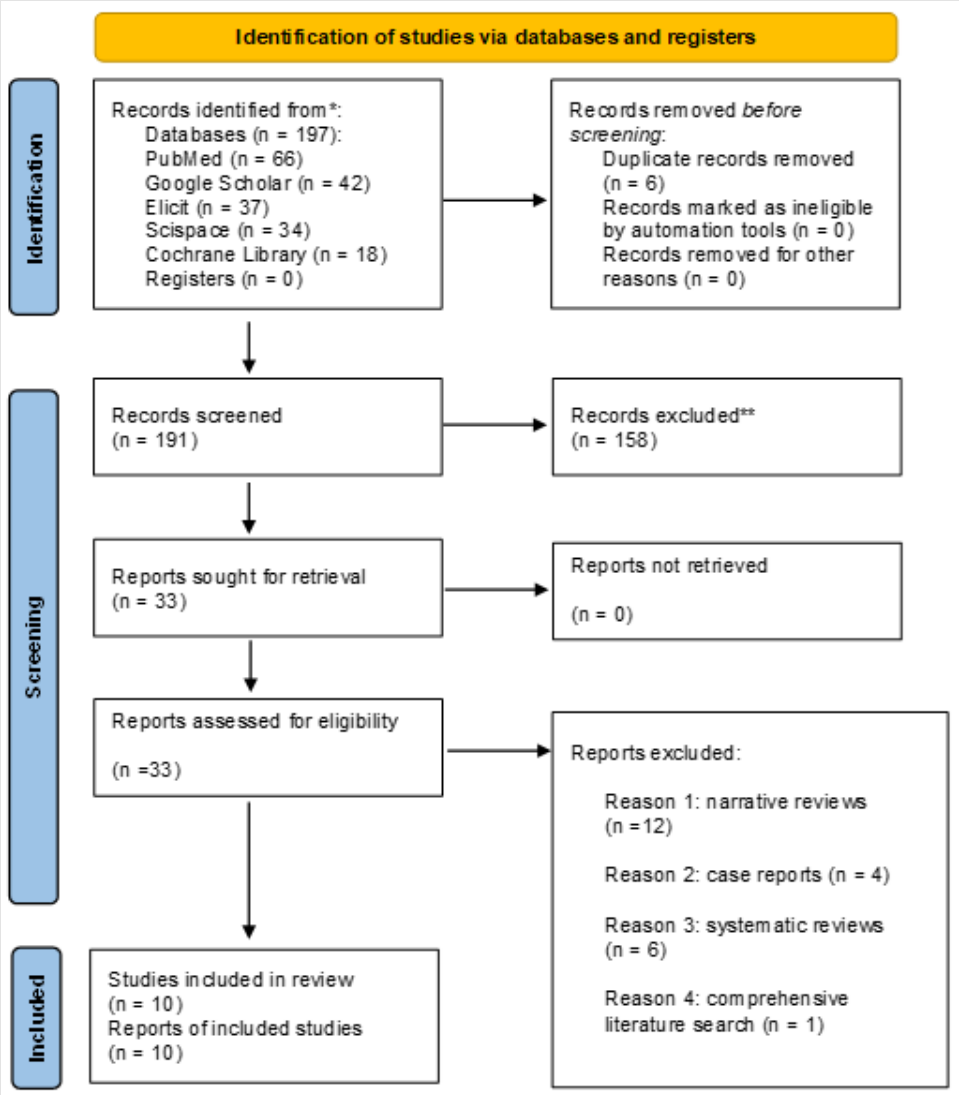

Figure 1: PRISMA Flow Diagram.

Table 1: Study Outcomes Table.

Study Citation	Pain Levels Outcome	Limb Salvage Outcome
Kilchukov, et al. [6]	HF-SCS: produced significantly greater pain relief by WIQ; at 3 months ($p < 0.001$) and 12 months ($p = 0.009$). HF-SCS: mean VAS score 2.8 LF-SCS: Mean VAS score 3.3, respectively ($p = 0.031$).	10 months after LF-SCS implantation: Only 1 patient (2%) required above-the-knee amputation.
Piedade, et al. [13]		The probability of limb survival for all 71 patients: 72% at 12 months. Mean limb survival time: 23.3±1.86 months
Klinkova, et al. [23]	Pain intensity reduction: significant decrease one year after SCS, from 8 (7-8) to 2 (2-4) points (P=0.002)	One-year follow-up after SCS: The leg salvage rate was 96.2%. An increase in motor activity improved the functional state of the microvasculature.

Cucuruz, et al. [32]	Pain reduction: significant decrease on the 10-point VAS scale from baseline (median = 7.5, IQR = 7-8) to follow-up at 2 years (median = 0, IQR 0-2.75), p < 0.001.	Limb salvage was achieved in a high percentage of cases; 30 out of 34 patients (88%). Increased mobility due to pain reduction.
Cyrek, et al. [43]	Pain intensity decreases on VAS: At Baseline: 81 mm +- 7. at 3 months: 45 mm +- 17. at 6 months: 23 mm +- 16. at 12 months: 16 mm +- 15 (p < 0.001 for all time points).	At 3 months of follow-up: all patients with Fontaine grade III showed Fontaine grade improvement from stage III to stage II or I. At 1-year of follow-up: limb salvage was achieved in all but 1 patient (97%; 28/29). 15 patients had limb ulcers (Fontaine stage IV); complete closure occurred in (73;11/15).
Tshomba, et al. [44]	Pain intensity evaluation: with the visual analog scale (VAS). pain reduction effects: stimulates patients to walk. Functional clinical success: an improvement in pain-free walking distance of at least 30 meters was reported in 25.7% of cases.	Follow-up period to record pain relief and limb survival: 1, 6, and 12 months for a mean follow-up period of 32 (range 14-41) months. The major amputation rate: 5.9% The minor amputation rate: 6.9%.
Liu, et al. [45]	Pain reduction in the SCS patient group: VAS score improvement one week (8.63 ± 0.54 vs. 4.48 ± 0.59, p < 0.001) and one year after SCS implantation (2.35 ± 0.62, p < 0.001). Non-SCS treatment group: the VAS score (7.98 ± 0.43, p = 0.020) and all other outcomes worsened at the one-year follow-up.	After SCS implantation: Lower limb 201Tl scintigraphy revealed that microcirculation intensity increased in the lower extremities.
De Caridi, et al. [46]	Group A: achieved complete pain relief. Group B: pain relief was observed.	Healing rates: Group A: 100% group B: 78% group C: 57% group D :88%. Incomplete healing: Group B: incomplete healing of one patient and one failure of SCS with amputation of the lower limb. Group C: incomplete healing in one patient and two cases of SCS removal in two pts after 5 and 8 months, with amputation of the lower limb.
Özdemir, et al. [47]	The VAS scores of the patients before and after SCS were examined. Before SCS: VAS score was 8 (min: 6; max: 10) After SCS: 1) The mean VAS values decreased by 3.32 (standard: 2.26) units. 2) A decrease in VAS value was observed in 85.5% of the patients, VAS dropped to median 4.5 (min: 1; max: 8)	
Kumar, et al. [48]	Among 313 patients who underwent a trial SCS implant, 263 patients (28 PAD) achieved 50% pain relief. VAS score Before SCS: 8.8 VAS score 6 months after SCS: 5.3.	

Data Collection Process

Two individuals extracted the data and categorized them in a table manually and independently; as shown in the (Appendix Table 1), by reading the reports twice interchangeably for each study to make sure they did not miss any data or make any mistakes, if any additional data was discovered during the double-checking, it was added in blue color; as demonstrated in the (Appendix Table 2), to indicate that it was discovered after the second review of the study.

Appendix Table 1: Initial Characteristics Table.

Study Citation	Study design	Case Number	Treatment Duration	Disease Type
Kilchukov, et al. [6]	RCT (randomized clinical trial)	56 (50)	(3 and) 12-month follow up post operation.	CLTI
Piedade, et al. [13]	Retrospective (cohort) study	71	follow-up of 17.1 ± 10.5 months.	Non reconstruct able-CLI
Asimakidou, et al. [30]	systematic review	Multiple (A total of 404 records were identified and finally 6 randomized controlled trials (RCTs), a Cochrane review and a meta-analysis were included in this systematic review.)	no specific time, it differed according to each groups' analysis.	PAD, PVD and CLI
Ertilav, et al. [36]	Case report	two cases, each included 1 patient		Ischemic pain
Marco, et al. [40]	comprehensive literature search			PAD
Klinkova, et al. [23]	prospective cohort study	56	Participants were recruited between August 2014 and December 2016 with a follow-up check after 12 months.	CLI
Ipema, et al. [31]	systematic review	More than 20 patients. (multiple)	follow-up of 69 months. Multiple	CLTI
Cucuruz, et al. [32]	retrospective analysis	34	follow-up at 2 years.	PAD
Cyrek, et al. [43]	Retrospective Analysis	29	Patient assessments before intervention, at discharge, after 3, 6, 12 and 24 months, and annually thereafter. Minimum follow-up period of 30 months	CLTI
Mekhail, et al. [32]	Systematic Review Based on Randomized Clinical Trials (RCTs)	multiple	Assessments were done at 6 months, 2 years, and 5 years.	Ischemic pain (CLI)
De Caridi, et al. [39]	Case report	3		CLI
Abu Dabrh, et al. [33]	Systematic review	2779	1 year of follow-up.	CLI
Tshomba, et al. [44]	Retrospective analysis	101	Treatment from 1995 to 2012 Median follow-up was 69 months (range 1-202 months)	CLI
Deogaonkar, et al. [17]	narrative review	multiple	12-month follow-up Minimum follow up of 18 months	PVD
Yılmaz, et al. [37]	Case report	1	1 month follow-up.	PAD
Liu, et al. [45]	retrospective case-controlled study	78 (37 received SCS)(41 did not receive SCS treatment.)	Patients received SCS implantation within 1 month. And got a one-year follow-up period to assess the outcomes.	CLI
Shamji, et al. [18]	Narrative review			
Lee, et al. [19]	Narrative review			

De Caridi, et al. [46]	observational study	30 (Among 564 patients of 4 groups, 34 patients were suitable for SCS)	2 weeks, 1, 3, 6 months, 1 year, and then yearly.t	PAD, CLI
De Caridi, et al. [38]	case report	1	1, 12 months	Hand ischemia
Deer, et al. [20]	narrative review			
Song, et al. [21]	narrative review			
Naoum, et al. [22]	narrative review	8 to 444 (categorized as randomized patients in multiple studies)	Up to 18 months	CLI, PAD
Ubbink, et al. [34]	systematic review	450 patients in six studies	12 to 24 months	NR-CCLI
Shabalov, et al. [26]	narrative review			
Kapural, et al. [24]	narrative review			
Meier, et al. [25]	narrative review			
Kinfe, et al. [35]	meta-analysis	752 patients Short-term 241 patients Medium-term 272 patients Long-term 239 patients	short-term (3 months), medium-term (3 to 11 months), and long-term (12 to 60 months)	PVD and rAP
Özdemir, et al. [47]	Retrospective study	62 patients	february 2011-january 2015	Multiple including PVD
Kumar, et al. [48]	economic evaluation	Multiple, PAD = 28 patients	6 months	Multiple including PAD
Rock, et al. [27]	Narrative review			
Pérez, et al. [28]	Narrative review			
Schulte, et al. [29]	Narrative review			

Appendix Table 2: Initial Outcomes Table.

Study Citation	Pain levels outcomes	Limb salvage outcomes
Kilchukov, et al. [6]	HF-SCS: mean VAS score 2.8 LF-SCS: Mean VAS score 3.3, respectively ($p = 0.031$).	Only 1 patient (2%) required above-the-knee amputation 10 months after LF-SCS implantation.
Piedade, et al. [13]		The probability of limb survival for all patients (n=71) was 72% at 12 months with a mean limb survival time of 23.3±1.86 months
Asimakidou, et al. [30]	Pain relief based on PRI was significantly less in the standard group ($p < 0.01$). Patients treated with SCS received significantly less narcotic and non- narcotic drugs. VAS score-significant long term pain relief ($p < 0.05$) in the SCS but not in the control group throughout follow-up.	Limb salvage after 12 months was significantly higher in the SCS group. – RR=0.74, 95% CI= 0.56 to 0.90. – RD= –0.11, 95% CI= –0.20 to –0.02 (It seems that SCS reduces the risk for amputation at 12 months but this effect is rather small.) Hazard ratio for major or minor amputation in the SCS group compared with the standard group was 0.81 (95% CI= 0.47 to 1.42). The overall number of amputations at 6- month and 2-year follow-up did not differ significantly between the groups ($p > 0.05$) There was no statistically significant difference between groups in amputation frequency, Limb salvage rates at 18 months were 62% in the SCS group and 45% in the control group. No statistically significant difference, Major amputation in 6/20 patients of the Implant group versus 9/18 of the Control Group ($p =0.42$))
Ertilav, et al. [36]	Case1: His pain was 9/10 according to vizual analog scale (VAS) and according to Fontain classification he was accepted stage 4. VAS score was 4 at 2nd week follow up. Case2: At the 6 months follow-up, the VAS score was 4 (preoperative: 9).	Case1: The thumb of the left foot had been amputated.

Marco, et al. [40]		
Klinkova, et al. [23]	In the study group, pain intensity assessed using VAS was significantly reduced one year after SCS: from 8 (7-8) to 2 (2-4) points (P=0.002),	The leg salvage rate during one-year follow-up after SCS was 96.2%.
Ipema, et al. [31]	In the study group, pain intensity assessed using VAS was significantly reduced one year after SCS: from 8 (7-8) to 2 (2-4) points (P=0.002),	The leg salvage rate during one-year follow-up after SCS was 96.2%.
Ipema, et al. [31]	Patients reported a significant reduction in pain on the 10-point VAS scale from baseline (median = 7.5, IQR = 7-8) to follow-up at 2 years (median = 0, IQR 0-2.75), $p < 0.001$.	Limb salvage was enabled in a high percentage of cases and increased mobility due to pain reduction. Limb salvage was achieved in 30 out of 34 patients (88%).
Cyrek, et al. [43]	Patients reported a significant decrease in pain intensity on VAS from 81 mm +- 7 at baseline to 45 mm +- 17 at 3 months, to 23 mm +- 16 at 6 months, and to 16 mm +- 15 at 12 months ($p < 0.001$ for all time points).	At 3 months follow-up, all patients with Fontaine grade III showed Fontaine grade improvement from stage III to stage II or I. At 1-year, limb salvage was achieved in all but 1 patient (97%; 28/29). 15 patients had limb ulcers (Fontaine stage IV); complete closure occurred in 73% (11/15).
Mekhail, et al. [32]	7 RCTs evaluated pain relief or change in pain score by visual analog scale (VAS). Results showed a difference of 35.8% in primary outcome (50% pain relief) favoring the SCS group at 3 years' follow-up. results showed a 39% improvement in percentage of patients attaining at least 50% pain relief with SCS compared with conventional medical management at 6 months.	
De Caridi, et al. [39]	After SCS implantation and test stimulation, the pain was reduced by 50% on both the right and the left side in all our patients. The main indications for permanent SCS therapy after 1 week of test stimulation were represented by TcPO2 increase >75%, decrease of opiods analgesics use of at least 50% and a pain maintained to within 20-30/100 mm on VAS	
Abu Dabrh, et al. [33]		
Tshomba, et al. [44]	The protocol for treadmill exercise used in this study consisted of walking at 2.5 km/h and 0% grade. Pain intensity was evaluated with the visual analog scale (VAS). pain reduction stimulates patients to walk. Functional clinical success was reported in 25.7% of cases, It's defined as an improvement in pain-free walking distance of at least 30 meters.	All patients were scheduled for assessment at months 1, 6, and 12 for a mean follow-up period of 32 (range 14-41) months. At each follow up visit, limb survival, walking distance and pain amelioration were recorded. Major amputation rate was 5.9%, and minor amputation rate was 6.9%
Deogaonkar, et al. [17]	Good pain relief was reported in more than 85% of the patients and most patients also reported improvement of their ischemic symptoms. It has also been suggested that pain relief might relieve vasoconstriction.	SCS significantly improved multiple outcomes, such as exercise tolerance, limb salvage, and pain level in patients presenting with critical leg ischemia.
Yılmaz, et al. [37]	The pain score at rest reported on a 10-point Visual Analog Scale (VAS) was 8. After successful trial stimulation, permanent SCS implantation was performed, and the pain immediately decreased from VAS 8 to 3.	On physical examination, the pulses were diminished on the right side, and the left leg was amputated above the knee. improvement in peripheral coldness, wound healing, and limb mobility was observed
Liu, et al. [45]	the VAS score of patients in the SCS treatment group improved one week (8.63 ± 0.54 vs. 4.48 ± 0.59, $p < 0.001$) and one year after SCS implantation (2.35 ± 0.62, $p < 0.001$). the VAS score worsened in the non-SCS treatment group at the one-year follow-up (7.98 ± 0.43, $p = 0.020$).	lower limb 201Tl scintigraphy revealed that microcirculation intensity increased in the lower extremities of patients in the SCS treatment group after SCS implantation relative to that before SCS implantation. 10 of the 41 patients in the non-SCS treatment group required the use of wheelchairs, whereas none of the patients in the SCS treatment group required the use of wheelchairs.

Shamji, et al. [18]		
Lee, et al. [19]		
De Caridi, et al. [46]	Group A achieved complete pain relief, group B, pain relief.	group A healing rate 100%, group B of 78%, group C of 57% and group D of 88%. (Group B, incomplete healing of one patient and one failure of SCS with amputation of the lower limb. Group C, Incomplete healing in one patient and two cases of SCS removal in two pts after 5 and 8 months, with amputation of the lower limb.)
De Caridi, et al. [38]	complete hand pain relief	Complete wound healing
Deer, et al. [20]		
Song, et al. [21]		
Naoum, et al. [22]	significant pain relief	Significant limb salvage (a rise in tcpO2 of at least 15% after a trial of SCS resulted in a significant limb salvage of 77% at 18 months.)
Ubbink, et al. [34]	Pain relief significantly better after three and twelve months of SCS	Conflicted results (There is evidence to favor SCS over standard conservative treatment alone to improve limb salvage and clinical situations in patients with NR-CCLI.) (Several pre-clinical and clinical studies using SCS have been performed to investigate potential beneficial effects such as reduction in amputation rate, pain relief, and healing of ulcers. The most desired effect is limb salvage) (Some studies did not show a significant difference between groups in amputation frequency after 12, 18, or 24 months of follow up)
Shabalov, et al. [26]		
Kapural, et al. [24]		
Meier, et al. [25]		
Kinfe, et al. [35]	PVD patients experienced reductions in the VAS score (approximately 1.9 points reduction)	(In a study with 2-, 6-, 12-, and 18-months follow-up, SCS provided long-term pain relief, but limb salvage at 18 months was not significantly improved by SCS in this rather small study.)(A 2013 Cochrane Library review of the therapy found significantly higher limb salvage and lower analgesic consumption in PVD patients treated with SCS compared with patients managed conservatively)
Özdemir, et al. [47]	the mean VAS values before and after SCS were 3.32 (standard deviation: 2.26) units decreased. In addition, 85.5% of the patients had decrease in VAS value as: VAS score was 8 (min: 6; max: 10) before SCS, VAS after SCS dropped to median 4.5 (min: 1; max: 8)	
Kumar, et al. [48]	VAS score was 8.8, after 6 months VAS score is 5.3 (313 patients underwent a trial SCS implant. 263 patients achieved 50% pain relief on trial stimulation and were selected to undergo implantation of a permanent SCS system.)	
Rock, et al. [27]		
Pérez, et al. [28]		
Schulte, et al. [29]		

Data Items

Data was gathered and primarily classified into the Study design, Case number, Treatment duration, Disease type, Pain levels outcomes and Limb salvage outcomes; as illustrated in (Table 1).

Study Risk of Bias Assessment

The risk of bias during the initial stages of collecting the research was manually assessed, through double-checking the studies' eligibility during the data extraction phase. This included incomplete reporting of outcomes and an insufficient number of patients. Referring to (Figure 2), the Newcastle-Ottawa scale (NOS) risk of bias tool, was used to determine further bias, and OpenAI's GPT-4 was used to verify the bias test results as illustrated in (Figure 3).

Cohort Studies

Study Citation	Selection (Max 4)				Comparability (Max 2)	Outcome (Max 3)			Total (Max 9)
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Kilchukov et al. (2023) [11]	*	*	*		* Gender	*	*	*	7
Piedade et al. (2023) [12]	*	*	*	*	** Diabetes, Smoking	*	*	*	9
Klinkova et al. (2020) [13]	*	*	*	*	** Hypertension, Gender	*	*	*	9
Cucuruz et al. (2022) [14]	*		*	*		*	*	*	6
Cyrek et al. (2021) [15]	*		*	*	**Smoking(nicotine use), Diabetes	*	*	*	8
Tshomba et al. (2014) [16]	*		*	*	** Smoking, Diabetes	*	*	*	8
De Caridi et al. (2016) [18]	*	*	*	*	** Diabetes, Hypertension		*	*	8
Özdemir et al. (2016) [19]	*		*	*		*	*		5
Kumar et al. (2013) [20]	*	*	*	*		*	*	*	7

Case Control Studies

Study Citation	Selection (Max 4)				Comparability (Max 2)	Exposure (Max 3)			Total (Max 9)
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Liu et al. (2018) [17]	*	*	*	*	** Diabetes, Hypertension	*	*	*	9

Figure 2: NOS Table.

ChatGPT4 Cohort

Study Citation	Selection (Max 4)				Comparability (Max 2)	Outcome (Max 3)			Total (Max 9)
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Kilchukov et al. (2023) [11]			*	*	* Patient condition, Treatment types	*	*	*	6
Piedade et al. (2023) [12]	*		*	*	** Diabetes, Disease severity	*	*	*	8
Klinkova et al. (2020) [13]	*	*	*	*	**Lifestyle , Sex	*	*	*	9
Cucuruz et al. (2022) [14]			*	*		*	*	*	5
Cyrek et al. (2021) [15]			*	*		*	*	*	5
Tshomba et al. (2014) [16]	*		*	*	*Onset of the ulcer	*	*	*	7
De Caridi et al. (2016) [18]			*	*	*TcPO2	*	*	*	6
Özdemir et al. (2016) [19]	*		*	*	*Gender	*	*	*	7
Kumar et al. (2013) [20]	*	*	*	*	*Age, Sex	*	*	*	8

ChatGPT4 Case Control

Study Citation	Selection (Max 4)				Comparability (Max 2)	Exposure (Max 3)			Total (Max 9)
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Liu et al. (2018) [17]	*	*	*	*	**Age, Gender, Type of medication	*	*	*	9

Figure 3: GPT-4's NOS Table.

Effect Measures

The effect measures of the outcomes were given as they were reported in the individual studies; pain levels were reported using Visual Analog Scale (VAS) scores at different time points and follow-ups. Limb salvage outcomes were described as limb survival rates or the percentage of patients needing amputations, and some studies described successful limb salvage as improvements in Fontaine stage or ulcer healing rates.

Certainty Assessment

Certainty of evidence assessment was based on the Newcastle-Ottawa Scale (NOS) scores. Studies with a score of 7-9 were regarded as having 'high' certainty evidence, studies with a score of 5-6 had "moderate" certainty, and studies with a score of 0–4 had "low" certainty. This methodology is less comprehensive than more established methods such as GRADE but considering the limited resources and time the reviewers had, it was decided that this technique was the most feasible for the review.

Results

With reference to (Figure 1), twelve narrative reviews [17-28] were excluded since they may have a potentially higher level of bias and generally interpreted data older than 10 years with no statistical results. Six systematic reviews [29-34] were excluded due to the inclusion of studies older than 10 years and the overlap of data that may lead to bias. Four case reports [35-38] were excluded since they covered individual cases or a limited number of cases, considering them weak evidence to make use of. One comprehensive literature search [39] was excluded since it included a review of studies older than 10 years. The illustrated flow diagram template above has been derived from the PRISMA website [40]. Based upon the ten studies that have been gathered and examined, a total of 1079 patients were

demonstrated, of whom 538 were rejected after screening, 4 were excluded for local infection and malfunction purposes, and 41 were in a control group; thus, only 498 patients were eligible to undergo SCS implantation. Referring to (Tables 1 & 2), Kilchukov, et al. [6] conducted a Randomized Controlled Trial (RCT) with 50 participants, examining the use of High-Frequency versus Low-Frequency Spinal Cord Stimulation in the Treatment of Chronic Limb-Threatening Ischemia. Evaluating the outcomes of pain levels, limb salvage and quality of life. Piedade, et al. [41] conducted a retrospective study of 71 cases, assessing the use of spinal cord stimulation (SCS) in Non-Reconstructable Critical Limb Ischemia.

Table 2: Study Characteristics Table.

Study Citation	Study Design	Case Number	Treatment Duration	Disease Type
Kilchukov, et al. [6]	RCT (randomized clinical trial)	56 (6 were rejected after screening)	3 and 12-month follow up post operation.	CLTI
Piedade, et al. [13]	Retrospective cohort study	71	follow-up of 17.1 ± 10.5 months.	Non reconstruct able-CLI
Klinkova, et al. [23]	Prospective cohort study	56	Participants were recruited between August 2014 and December 2016 with a follow-up check after 12 months.	CLI
Cucuruz, et al. [32]	Retrospective analysis	34	follow-up at 2 years.	PAD
Cyrek, et al. [43]	Retrospective Analysis	29	Patient assessments before intervention, at discharge, after 3, 6, 12 and 24 months, and annually thereafter. Minimum follow-up period of 30 months	CLTI
Tshomba, et al. [44]	Retrospective analysis	101	Treatment from 1995 to 2012 Median follow-up was 69 months (range 1-202 months)	CLI
Liu, et al. [45]	retrospective case-controlled study	78 (37 received SCS) (41 did not receive SCS treatment.)	Patients received SCS implantation within 1 month. And got a one-year follow-up period to assess the outcomes.	CLI
De Caridi, et al. [46]	observational study	Among 564 patients, 34 patients were suitable for SCS, 30 completed the study.	2 weeks, 1, 3, 6 months, 1 year, and then yearly.	PAD, CLI
Özdemir, et al. [47]	Retrospective evaluation	62 patients	February 2011-january 2015	Multiple including PVD
Kumar, et al. [48]	economic evaluation	Multiple, PAD = 28 patients	6 months	Multiple including PAD

Evaluating the outcomes of limb salvage. Klinkova, et al. [42] conducted a prospective cohort study on 56 cases, evaluating the clinical outcomes of pain levels, limb salvage and quality of life in patients with Critical Limb Ischemia one year after spinal cord stimulation. Cucuruz, et al. [43] conducted a retrospective analysis with 34 participants, examining the effects of neuromodulation on Peripheral Artery Disease. Evaluating the outcomes of pain levels, limb salvage and quality of life. Cyrek, et al. [44] conducted a retrospective analysis on 29 cases, exploring the use of spinal cord stimulation in improving limb salvage for Chronic Limb-Threatening Ischemia. Evaluating the outcomes of pain levels, limb salvage and quality of life. Tshomba, et al. [45] conducted a retrospective analysis with 101 participants, evaluating the effects of spinal cord stimulation on pain levels, limb salvage and quality of life outcomes in patients with Critical Limb Ischemia. Liu, et al. [46] conducted a retrospective case-controlled study with 78 participants, evaluating the effects of spinal cord stimulation on pain levels, limb salvage and quality of life outcomes in patients with Critical Limb Ischemia. De Caridi, et al. [47] conducted an observational study with 34 participants, evaluating the effects of spinal cord stimulation on pain levels, limb salvage and quality of life outcomes in patients with Critical Limb Ischemia. Özdemir, et al. [48] conducted a retrospective evaluation with 62 participants, evaluating the effects of spinal cord stimulation on pain levels and quality of life outcomes in patients with Peripheral Vascular Disease.

Kumar, et al. [49] conducted an economic evaluation of SCS on various diseases including 28 PAD patients, evaluating the effects of spinal cord stimulation on pain levels, limb salvage and quality of life outcomes in patients with Peripheral Arterial Disease. The risk of bias was collaboratively assessed using the Newcastle-Ottawa Scale (NOS), whose scores range from a scale of 0 to 9, studies scoring 7

to 9 were considered 'Low' in bias and high quality, scoring 5 to 6 was considered 'Moderate' in bias and quality, scoring 0 to 4 was considered 'High' in bias and thus poor in quality (Figure 2). OpenAI's GPT-4 was used as a third-party auditor to verify the test scores [50]. The difference between the authors' and GPT-4's scores was 1 point in five studies [6, 41-48]. 2 points in two studies [47,49], and the same score in Klinkova, et al. [41,45]. For some reason, GPT-4 couldn't read the part where Cyrek, et al. [44] demonstrated the comorbidities and characteristics of the patients, and that resulted in subtracting two points from its score making the difference 3 points for this study. After correcting this error, the overall average similarity with GPT-4's scores were 88.9% (Figure 3). Based upon the ten studies that have been gathered and examined, and throughout the data extraction process that was tabulated, Pain levels were reported mostly by using Visual Analog Scale (VAS) scores at different follow up timings, Overall outcomes showed significant pain relief over time.

Also, Limb salvage outcomes were described as limb survival rates over time or the percentage of patients requiring amputations. Some studies described successful limb salvage as improvements in Fontaine stage or ulcer healing rates; overall outcomes showed positive limb salvage results over time.

Discussion

In this systematic review, 191 research articles were screened, and 10 articles were selected for inclusion, providing information on pain levels and limb salvage outcomes in patients with peripheral arterial disease (PAD) treated with spinal cord stimulation (SCS). However, several limitations were encountered throughout the review process, including difficulties accessing the EMBASE database, limitations in the NOS bias assessment test, unavailability of full-text reports in some studies, errors in content generated by GPT-4, data heterogeneity, and time constraints. In light of the presented evidence from various systematic reviews, including Asimakidou, et al. [29,31,33,34], the interpretation of the results suggests that spinal cord stimulation (SCS) shows great potential as an effective treatment for managing chronic pain of ischemic origin and preserving the affected limbs, particularly in patients with critical limb ischemia (CLI), peripheral arterial disease (PAD) and peripheral vascular disease (PVD). Moderate to high quality evidence that tonic SCS is effective in non-reconstructable CLI patients was brought up by Asimakidou, et al. [28]. According to study findings, SCS promotes limb salvage, pain relief and improved quality of life in this patient population. Mekhail, et al. [30] demonstrated moderately strong evidence supporting the use of SCS in patients with critical limb ischemia. SCS was associated with improved functional status and decreased utilization of analgesic medications.

Additionally, it showed efficacy in both pain reduction and quality of life. Ubbink, et al. [33] found that SCS significantly improved limb salvage after 12 months compared to standard conservative treatment alone. The SCS group also experienced significant pain relief and reduced analgesic usage. Also, significantly more patients reached Fontaine stage II than in the conservative group, which shows the effectiveness of SCS on the overall clinical outcomes. The study by Kinfe, et al. [34] revealed that SCS treatment provided long-term pain relief with a relatively low complication rate in patients with ischemic pain. Additionally, PVD SCS-treated patients showed significant reductions in the visual analog scale (VAS) score, showing positive effects of SCS. The purpose of this systematic review was to gain insights into the efficacy of SCS in the relief of pain and limb salvage for patients with PAD in the past 10 years. The findings showed great results in terms of pain relief and limb salvage. They highlight the efficacy and safety of SCS in patients with CLI, PAD and PVD. Moreover, they show a huge potential for SCS to be used as a first-line treatment for such conditions. Considering recent advances in neuromodulation, the results presented have shed light on the importance of considering SCS as a promising therapeutic option, revealing significant insights and aiming to have a positive impact on the medical research field and healthcare industry. First, all studies indicated significant pain relief over time, apart from Piedade, et al. [41], that neglected to investigate pain level outcomes.

Pain levels were assessed using the Visual Analog Scale (VAS) in the following studies: Kilchukov, et al. [6,42-43-44-46-49]. Tshomba, et al. [45] also utilized VAS to evaluate pain levels while walking on a treadmill, but specific scores were not provided. Instead, they defined Functional clinical success in 25.7% of the cases as pain-free walking distance of at least 30 meters. In contrast, De Caridi, et al. [47] described pain relief narratively without using any specific assessment method or presenting statistical evidence. It is recommended for future studies to standardize a single tool for pain levels assessment such as the Visual Analog Scale (VAS), The use of a standardized test ensures data consistency and allows for future meta-analysis. Limb salvage outcomes were defined as long-term limb survival rates or the percentage of patients who needed amputations. Some studies defined efficient limb salvage as improvements in Fontaine stage Cyrek, et al. [44] or ulcer healing rates Cyrek, et al. [47-46] described it as increased microcirculation intensity in the lower extremities. Within adequate follow-up durations, SCS demonstrated improvements in limb salvage rates, as given in the studies: Kilchukov, et al. [6,41-49].

Generally, limb amputation rates were very limited, with one patient (2%) requiring above-the-knee amputation in Kilchukov, et al. [6]. limb salvage was achieved in all but 1 patient in Cyrek, et al. [44]. The major amputation rate was 5.9%, and the minor amputation rate was 6.9% in Tshomba, et al. [45]. The incomplete healing of one patient and one failure of SCS with amputation of the lower limb in De Caridi, et al. [47]. General outcomes revealed favorable limb salvage results over time in all studies except Özdemir, et al. [48-49], where limb salvage outcomes have not been assessed. It would be recommended for future research to make use of artificial intelligence tools

to predict the effectiveness of SCS for each patient individually before the case worsens enough to require limb amputation and to standardize the assessment of limb survival.

Limitations

In the systematic review, limitations were encountered in accessing the EMBASE database. The database redirected researchers to their university website. Upon logging in, another redirection to EMBASE occurred, accompanied by a denial message and a request to choose an alternative method, the only available alternative method was still connecting through the university, resulting in the researchers being unable to access the EMBASE database. Despite the fact that the NOS bias assessment test is known to be applicable to cohort studies and case-control studies only, where patients are classified into exposed and non-exposed groups, it was found practical for other study designs, considering its straight-forward and generalized format of questions, and due to the limitations of time and resources, it was the most feasible test to implement. In addition to that, some cohort studies revealed a comparison between exposed groups who had different Fontaine stages instead of revealing both exposed and non-exposed groups. To further justify our bias assessment, some studies did not enable access to the full text; for that reason, the bias test conducted on them might not be fair enough to assess their level of bias. Limitations were encountered with GPT-4 as a bias verification auditor. The character limit in the model posed a challenge, as some studies exceeded its capacity, necessitating the splitting of the text into multiple prompts. However, when providing all parts and requesting the bias test, the model failed to comprehend the instructions and instead focused on explaining the study without conducting the bias test.

Despite multiple attempts using various prompts and approaches to convey the split study and bias test, it took several tries to successfully complete the verification. Another limitation was the imposed restriction of 25 messages per 3 hours. As the model struggled to understand prompts and fulfill requests accurately, we frequently reached this cap, resulting in 1-2 waiting hours for the limit to reset. Moreover, the model occasionally provided generalized answers that did not address the specific question options, leading to incorrect scoring. Additionally, after completing the test for some studies, there were instances of incorrect calculation of the total score. Also, the model sometimes awarded 2 points instead of 1 for certain questions, which then affected the overall score calculation. To ensure accurate scoring, we carefully logged GPT-4's answers and correctly documented the scores in the GPT-4 bias test verification table provided in (Figure 3). The whole conversation with GPT-4 regarding the bias test verification has been provided by referring to the link [49]. Due to time constraints, limited availability of eligible studies to conduct a meta-analysis, as well as data heterogeneity, the reviewers were unable to perform a meta-analysis, statistical synthesis, assessment of reporting bias, evaluation of certainty, and calculation of effect measures. For Özdemir, et al. [48], which was published in Turkish, we relied on Google Translate and GPT-4 for translation and data extraction.

For future reviews, it is recommended to utilize artificial intelligence (AI) models such as OpenAI's GPT as an assistant for general tasks like bias test verification, as demonstrated in this study. However, it is advisable to double-check the generated outputs when interpreting the results and statistical answers of the AI model, as inaccuracies and mistakes may occur.

Conclusion

This systematic review has investigated the effectiveness of spinal cord stimulation technology on pain levels and limb salvage in patients with peripheral arterial disease, titled "Spinal Cord Stimulation in Peripheral Arterial Disease: A 10-Year Systematic Review of Pain Relief and Limb Salvage Outcomes". All the demonstrated work has been done collaboratively. Several key findings have been addressed regarding the implementation of SCS as a treatment, such as the significant pain relief outcomes along with positive limb salvage outcomes. SCS has been demonstrated to be effective and safe in individuals with PAD, PVD, and CLI. However, several important limitations have also been identified and further discussed. As indicated in this study, it is advised for future reviews to use artificial intelligence (AI) models such as OpenAI's GPT to provide aid for general tasks such as verifying bias tests. Further, it is recommended to double-check all outputs when evaluating the AI model's results and statistical responses, given that flaws and inaccuracies may arise. It is also suggested that future studies use a single method for assessing pain levels, such as the Visual Analog Scale (VAS), and implement a standardized test to assess limb salvage as well, which ensures uniformity of results and enables future meta-analysis. Eventually, it would be encouraged for future research and health professionals to employ artificial intelligence tools to anticipate the effectiveness of SCS for each patient individually before the condition deteriorates to the point where limb amputation becomes necessary.

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Conflict of Interest

This study was not registered in a review registry, and no protocol was prepared. It received neither financial nor other support, and no external funders or sponsors were involved. We declare that we have no competing interests that could influence the findings. All the data presented in this study is publicly available and can be found through the references' links and the full-text reports.

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