Consistent outcomes from multiple RCTs support SCS for the treatment of painful DPN

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Introduction

Diabetic peripheral neuropathy (DPN) is the most common neuropathic syndrome seen in patients with diabetes. DPN symptoms can include stabbing or burning pain eventually progressing to numbness in the lower extremities resulting in loss of protective sensation. Traditionally, pain associated with DPN has been pharmacologically treated with gabapentin/pregabalin, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors[1]. These treatment approaches are often unsuccessful in the long-term, with many painful DPN patients abandoning initial prescription analgesics within months[1]. Spinal Cord Stimulation (SCS) has been examined in 3 randomized controlled trials (RCTs)[2,3,4] comparing SCS to conventional medical management (CMM).

Objectives

We reviewed the evidence presented in three RCTs to assess the effectiveness of SCS therapy for the treatment of painful DPN.

Materials & Methods

Three RCTs[2,3,4] comparing SCS to CMM for the treatment of painful DPN were compared and contrasted by primary outcome measures, primary endpoint duration, intervention, demographics, treatment-effect-size and quality-of-life outcomes based on the intention-to-treat principle (Table 1). Two RCTs[2,3] using traditional SCS programming were independently designed, conducted and reported, with industry grant support, in western Europe. One RCT[4] using high frequency SCS programming was industry-sponsored and conducted in the United States. Primary outcome measures included a composite primary endpoint where patients could be identified as treatment responders by reduction in pain diary scores or Patient Global Impression of Change, ≥50% reduction in VAS measurement for pain, and a compound primary endpoint of ≥50% reduction in pain score and no neurologic decline. EQ-5D questionnaires were used to assess Quality of Life. Primary endpoint duration was 6 months in two studies[2,3] and 3 months in one study[4].

Results

Treatment effect size is a published way to look at the effect of an intervention for DPN, used by the American Academy of Neurology (AAN)[10]. A difference >20% is considered a large treatment effect. The difference in treatment effect size between SCS and control groups for the primary endpoint in the Intention-to-Treat populations ranged from 52% to 58% (Table 1, Figure 1). Improvement in EQ-5D Quality of Life (QoL) index scores at 6 months ranged from 0.124 to 0.380, with an average (SE) improvement from baseline of 0.26 (0.07) at 6-months and 0.24 (0.09) at 12-months (Figure 1). The studies of traditional SCS[2,3,6] show greater and sustained improvement in QoL than the study of high frequency SCS[7] (Figure 2).

Table 1. Study Design and Treatment Effect

	Slangen et al (2014)[2]	de Vos et al (2014)[3]	Petersen et al (2021)[4]; Clinical Summary[5]
Study Logistics and Design			
Sponsor	Maastricht University Medical Center (NCT01162993)*	Medisch Spectrum Twente (ISRCTN03269533)**	Nevro
Study Device Manufacturer	Medtronic	St. Jude/Abbott	Nevro
# of Centers (Countries)	2 (Netherlands)	7 (Netherlands, Denmark, Belgium, Germany)	18 (United States)
Design	RCT	RCT	RCT
SCS Programming	Traditional SCS	Traditional SCS	10 kHz SCS
Comparator	Best medical treatment	Best medical therapy	Conventional medical management
Primary endpoint (months)	6	6	3
Population	Refractory DPN	Refractory DPN	Refractory DPN
Sample Size	36	60	216
% Subjects with Type 2 Diabetes	Control arm = 93 SCS arm = 86	Control arm = 75 SCS arm = 75	Control arm = 97.1 SCS arm = 92.9
Mean (SD) HbA_{1c}, % at Baseline	Control arm = 8.4 (2.7) SCS arm = 8.3 (2.0)	NA	Control arm = 7.4 (1.2) SCS arm = 7.3 (1.1)
Study Outcomes			
Primary Endpoint Definition (all randomized subjects; ie, ITT):	≥ 50% pain reduction during daytime or nighttime or a score of ≥ 6 on a 7-point Likert scale of the PGIC scale for pain and sleep	> 50% pain reduction	≥ 50% pain relief without a meaningful worsening of baseline neurological deficits
SCS Responder Rate	59%	63%†	66.4%††
Control Responder Rate	7%	5%	11.7%††
Treatment Effect Size‡	**52%**	**58%**	**55%**

ITT = intention-to-treat, PGIC = Patient Global Impression of Change
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**Support (grant) was sponsored by St. Jude Medical; St. Jude Medical was not involved in data analysis/interpretation or manuscript writing.
†Number calculated using the number of patients randomized to the SCS study group (n = 40) and the number of patients in the SCS study group with > 50% pain reduction (n = 25) at 6 months. The publication itself[3] reported a "> 50% pain reduction n (%)" of "25 (60%)" for the SCS study group (n = 40; randomized patients) at 6 months.
††Primary endpoint ITT responder rate as reported in the Nevro Clinical Summary and FDA Summary of Safety and Effectiveness Data. Petersen et al (2021) reported SCS and control responder rates of 79% and 5%, respectively ("ITT population with known status")[4].
‡Treatment effect size = SCS responder rate - control responder rate
‡‡EQ-5D values represent the baseline and follow-up scores on a scale of 0 to 1, with 1 = perfect health.

Figure 1. QoL Improvements in 3 RCTs

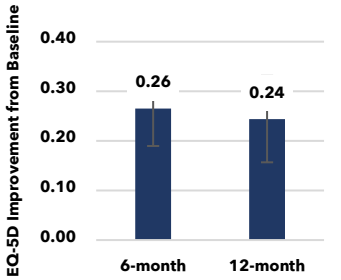
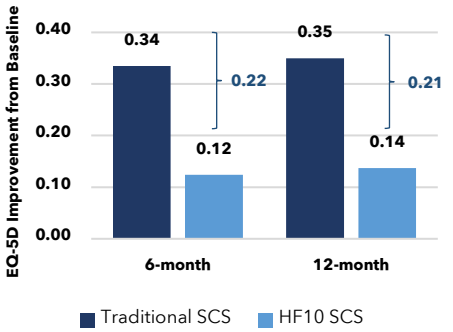


Figure 2. QoL Improvements by Waveform



Conclusions

Three RCTs[2,3,4] have all shown SCS as effective over CMM for treating DPN pain symptoms. The variety of primary endpoints were all meaningful measures of reduction in pain symptoms and ranged from pragmatic measures to measures that included neurological deterioration, though very few subjects regressed. Multiple RCTs have clearly established effectiveness of SCS therapy for the treatment of painful DPN. Patients from 1 study[4] have been followed-up to 18 months[8] and patients in another[2] up to 10 years[9] with similar outcomes, demonstrating long-term benefits of SCS for patients with painful DPN.

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