Sustained Treatment Effect of Spinal Cord Stimulation in Painful Diabetic Peripheral Neuropathy: 24-Month Follow-up of a Prospective Two-Center Randomized Controlled Trial

Maarten van Beek,[1] Rachel Slangen,[1] Nicolaas C. Schaper,[2] Catharina G. Faber,[3] Elbert A. Joosten,[1] Carmen D. Dirksen,[4,5] Robert T. van Dongen,[6] Alfons G.H. Kessels,[4] and Maarten van Kleef[1,7]

Diabetes Care 2015;38:e132–e134 | DOI: 10.2337/dc15-0740

Spinal cord stimulation (SCS) has been demonstrated to serve as a successful second-line treatment modality for painful diabetic peripheral neuropathy (PDPN), as documented in two randomized clinical trials (RCTs) (1,2). Besides the fact that these two RCTs demonstrate a pain-relieving effect for a period of 6 months after the start of SCS treatment, only small observational studies suggest a long-term sustained effect in PDPN (3–5). In this article, we present the 24-month follow-up data of our recently published RCT in *Diabetes Care* (1).

Thirty-six patients were enrolled in this study, and after randomization, 22 patients with PDPN in the lower limbs (15 male, mean age 57.1 years [SD 12.4], years of PDPN 6.0 [SD 5.1]) were assigned to the SCS group. A 2-week trial stimulation was performed to evaluate sufficient pain relief. After 6 months, 93% of patients in the control group crossed over to receive SCS. Treatment success of SCS was predefined in the protocol as ≥50% relief of pain intensity on a numeric rating scale (NRS) for 4 days during the daytime or nighttime or "(very) much improved" for pain and sleep on the patient global impression of change (PGIC) scale at 24 months. Additional outcome parameters were

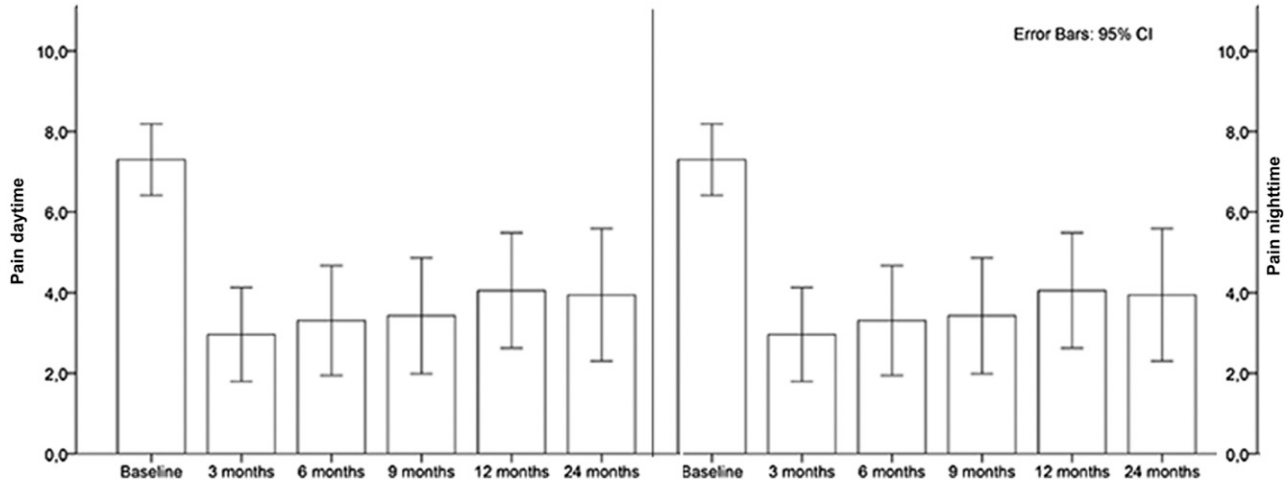

Figure 1—Mean pain scores at daytime and nighttime.

[1]Department of Anesthesiology and Pain Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands
[2]Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands
[3]Department of Neurology, Maastricht University Medical Centre, Maastricht, the Netherlands
[4]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, the Netherlands
[5]CAPHRI School for Public Health and Primary Care, Maastricht University, Maastricht, the Netherlands
[6]Department of Anesthesiology, Pain and Palliative Care, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
[7]Department of Anesthesiology, Free University of Amsterdam, Amsterdam, the Netherlands

Corresponding authors: Maarten van Beek, m.vanbeek@maastrichtuniversity.nl, and Maarten van Kleef, maarten.van.kleef@mumc.nl.

Received 9 April 2015 and accepted 7 May 2015.

Clinical trial reg. no. NCT01162993, clinicaltrials.gov.

assessed as previously described (1). The linear rate of change in postbaseline measurements was examined based on a random intercept regression model. A treatment success comparison between 6 and 24 months was performed using the McNemar test. Differences between baseline and follow-up data were analyzed by means of paired sample *t* tests.

Out of 22 patients, 17 patients (12 male, mean age 54.9 years [SD 11.5], years of PDPN 6.2 [SD 5.4]) underwent positive trial stimulation and were implanted with a permanent SCS device as described elsewhere (1). Mean pain scores during day and night decreased by 3.3 points at daytime ($P < 0.001$) and 3.2 points at nighttime ($P < 0.001$) at 24-month follow-up (Fig. 1). In total, eight (47%) and six (35%) patients reported a 50% pain reduction during day and night at 24 months, respectively. Clinically significant improvements on the PGIC for pain and sleep were reported by nine (53%) patients at 24-month follow-up. Treatment success of SCS was observed in 11 out of 17 patients (65%) (Table 1). No significant difference was observed in treatment

Table 1—Outcomes of patients with a positive trial stimulation in the SCS group up to 24 months: received treatment analysis

	Baseline	3 months	6 months	9 months	12 months	24 months
SCS received treatment group, *n*	17	16	16	16	16	15
HbA_{1c} (mmol/mol)†	66.4 ± 21.0	—	65 ± 15.3	—	58.4 ± 14.5	—
HbA_{1c} (%)†	8.2 ± 1.9	—	8.1 ± 1.4	—	7.5 ± 1.3	—
NRS score						
Day	7.3 ± 1.7	3.0 ± 2.2	3.3 ± 2.6	3.4 ± 2.7	4.1 ± 2.7	4.0 ± 3.0
Night	6.7 ± 2.2	2.9 ± 2.4	3.5 ± 3.0	3.3 ± 2.6	3.6 ± 2.7	3.5 ± 3.0
NRS ≥50% pain reduction, *n*/total *n* (%)						
Day	—	11/17 (65)	9/17 (53)	9/17 (53)	6/17 (35)	8/17 (47)
Night	—	7/17 (41)	8/17 (47)	10/17 (59)	9/17 (53)	6/17 (35)
PGIC, *n*/total *n* (%)						
Pain	—	15/17 (88)	12/17 (71)	10/17 (59)	11/17 (65)	9/17 (53)
Sleep	—	13/17 (76)	8/17 (47)	10/17 (59)	9/17 (53)	9/17 (53)
Treatment success, *n*/total *n* (%)	—	15/17 (94)	13/17 (76)	13/17 (76)	12/17 (71)	11/17 (65)
Modified Brief Pain Inventory–Diabetic Peripheral Neuropathy†						
Pain Severity Index	7.2 ± 1.6	3.5 ± 2.4**	3.3 ± 2.5**	4.1 ± 2.5**	4.2 ± 2.4**	4.8 ± 2.7
Pain Interference Index	6.3 ± 2.1	2.7 ± 2.1***	3.1 ± 2.3**	3.6 ± 2.6*	3.7 ± 2.5*	3.7 ± 2.8*
Neuropathic Pain Scale‡						
Deep pain	8.4 ± 1.7***	4.6 ± 3.1***	6.2 ± 2.8***	5.4 ± 2.9***	5.4 ± 2.9***	5.9 ± 2.9***
Surface pain	5.6 ± 3.6	3.6 ± 3.1	2.9 ± 3.0*	4.3 ± 3.2	3.2 ± 3.0**	3.2 ± 3.5
Intensity	8.0 ± 1.7	4.0 ± 2.6***	3.9 ± 2.9***	4.9 ± 3.0***	5.0 ± 2.7***	5.7 ± 2.6***
Unpleasantness	8.1 ± 1.8	4.9 ± 2.9***	5.3 ± 2.8***	5.7 ± 3.0**	5.6 ± 2.9***	6.1 ± 3.1*
Coldness	3.3 ± 3.5	2.5 ± 3.1	2.3 ± 2.9	2.4 ± 2.7	2.7 ± 2.7	3.3 ± 3.1
Hotness	6.5 ± 3.0	2.1 ± 2.7***	2.5 ± 3.2***	2.7 ± 3.1***	3.5 ± 3.2***	3.9 ± 3.3***
Dullness	7.7 ± 2.2	4.1 ± 2.7***	4.4 ± 3.6**	4.6 ± 3.3***	5.1 ± 3.2**	6.3 ± 2.8
Sharpness	8.1 ± 2.2	3.8 ± 3.2***	4.8 ± 3.4**	5.0 ± 2.9***	5.4 ± 3.1**	5.8 ± 2.9*
Sensitivity	7.7 ± 2.6	3.8 ± 2.4***	4.7 ± 3.0**	4.3 ± 2.9***	4.3 ± 2.9**	3.5 ± 3.5***
Itching	3.2 ± 3.1	1.4 ± 2.1	1.3 ± 2.2*	1.9 ± 2.9	1.4 ± 2.3	1.7 ± 2.7
EuroQol-5 Dimension Questionnaire§						
Utility scores	0.27 ± 0.31	0.60 ± 0.29***	0.56 ± 0.27**	0.58 ± 0.26***	0.62 ± 0.32***	0.40 ± 0.36
Current health	55.3 ± 17.1	65.1 ± 13.2*	60.6 ± 20.3	66.1 ± 12.3*	64.7 ± 11.3	59.3 ± 20.6
Medical Outcomes Study Short-Form 36‖						
Mental component score	43.1 ± 14.2	51.6 ± 10.9**	49.6 ± 12.0*	49.1 ± 12.2*	49.1 ± 12.3*	50.4 ± 14.7
Physical component score	27.0 ± 7.6	33.7 ± 8.4**	32.6 ± 9.7	35.1 ± 9.1*	32.8 ± 8.7*	31.9 ± 7.6*
Medical Outcomes Study Sleep Scale¶						
Sleep Problems Summary 9	57.0 ± 13.9	36.4 ± 18.5***	38.5 ± 17.3***	42.4 ± 16.5**	43.7 ± 18.1*	43.8 ± 16.2**
Quantity of sleep, h	5.0 ± 1.8	6.6 ± 2.0*	6.5 ± 1.8*	6.6 ± 1.8*	6.3 ± 2.2	6.4 ± 1.9
Optimal sleep, *n*/total *n* (%)	3/17 (18)	5/17 (29)	3/17 (18)	3/17 (18)	2/17 (12)	4/17 (24)
Beck Depression Inventory#	13.6 ± 7.8	11.4 ± 8.8*	12.0 ± 9.0	9.9 ± 8.6***	12.5 ± 8.4	12.8 ± 10.4

Data are mean ± SD, unless otherwise noted. †Assesses the severity of pain and its impact on daily functioning and forms two composite scores, the Pain Severity Index and the Pain Interference Index. 0 means "nonpain'" or "does not interfere" and 10 is "pain as bad as you can imagine" or "completely interferes." ‡Includes two items that assess the global dimensions of pain intensity and unpleasantness and eight items that assess the specific qualities of neuropathic pain, in which 0 is "no pain or not" and 10 is "the most sensation imaginable." §The EuroQol-5 Dimension Questionnaire is a health status measure with respect to mobility, self-care, usual activities, pain or discomfort, and anxiety or depression (no problems, some problems, and extreme problems). A utility score of 1 represents "perfect health," 0 represents "death," and less than 0 "worse than death." Self-rated current health status was assessed using a vertical visual analog scale on which 0 indicates worst possible health and 100 indicates perfect health. ‖Measures physical and mental component scores, converted to a 0–100 scale, with higher scores indicating higher levels of functioning or well-being. ¶Measures sleep quality and quantity. Sleep Problems Summary 9 scores range from 0–100 and higher scores indicate worse outcomes. #Severity of depression was measured by the Beck Depression Inventory, and higher total scores indicate more severe depressive symptoms. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ compared with baseline.

success rate at 24-month follow-up (65%) compared with treatment success rate at 6-month follow-up (76%).

During the follow-up period, a new pulse generator was implanted in two patients, and four patients had a revision of the stimulation lead. One patient withdrew due to an infection and removal of the SCS system after 6 weeks. At 24-month follow-up, one patient did not respond to the questionnaires, resulting in available data of 15 patients.

In conclusion, the data of this prospective two-center RCT demonstrate a sustained effect of SCS on pain relief in PDPN after 24 months.

Acknowledgments. The authors would like to acknowledge the patients who participated in the study. Furthermore, the authors would like to thank the members of the multidisciplinary steering committee for designing and guiding the protocol.

Duality of Interest. This work was supported by a grant from Medtronic for the employment of one researcher (R.S.) for 3 years. No other potential conflicts of interest relevant to this article were reported.

Medtronic was not involved in the analysis and interpretation of the data.

Author Contributions. M.v.B. contributed to the analysis and interpretation of the data and wrote the manuscript. R.S. contributed to the study design and analysis and interpretation of the data. N.C.S., C.G.F., E.A.J., C.D.D., and R.T.v.D. contributed to the study design. A.G.H.K. contributed to the study design and analysis of the data. M.v.K. contributed to the study design and interpretation of the data and reviewed the manuscript. M.v.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Slangen R, Schaper NC, Faber CG, et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care 2014;37:3016–3024

2. de Vos CC, Meier K, Zaalberg PB, et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. Pain 2014;155:2426–2431

3. Daousi C, Benbow SJ, MacFarlane IA. Electrical spinal cord stimulation in the long-term treatment of chronic painful diabetic neuropathy. Diabet Med 2005;22:393–398

4. Slangen R, Pluijms WA, Faber CG, Dirksen CD, Kessels AG, van Kleef M. Sustained effect of spinal cord stimulation on pain and quality of life in painful diabetic peripheral neuropathy. Br J Anaesth 2013;111:1030–1031

5. Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet 1996;348:1698–1701