2018

Is spinal cord stimulation an effective therapy to treat severe lower extremity painful diabetic peripheral neuropathy that has lasted over one year and has not responded to medical therapy?

Eleni Brecht
Philadelphia College of Osteopathic Medicine

Is spinal cord stimulation an effective therapy to treat severe lower extremity painful diabetic peripheral neuropathy that has lasted over one year and has not responded to medical therapy?

Eleni Brecht, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 15, 2017

Abstract

Objective: The objective of this selective EBM review is to determine whether or not "Is spinal cord stimulation an effective therapy to treat severe lower extremity painful diabetic peripheral neuropathy that has lasted over one year and has not responded to medical therapy?"

Study Design: A review of two RCTs and one case series published in English in 2014.

Data Sources: Two RCTs and one case series found via PubMed that evaluated the benefit of spinal cord stimulation (SCS) versus best medical treatment (BMT) to treat severe painful diabetic peripheral neuropathy (PDPN).

Outcome(s) Measured: The amount of pain a patient experiences, measured using either a visual analogue scale with 0 representing no pain and 100 representing the worst pain imaginable, or measured with a numeric rating scale.

Results: All three studies found a significant decrease in pain levels in patients receiving SCS treatment for severe PDPN compared to patients receiving BMT. In the Abd-Elsayed et al. case series, a patient with PDPN reported a 60% overall decrease in pain 1 month post SCS implantation. In the De Vos et al. RCT, the average visual analogue scale (VAS) pain score in patients receiving SCS was reduced from 73/100 to 31/100 ($P < 0.001$), while the VAS pain score in the control group remained 67/100. 60% of patients in the SCS group experienced at least 50% pain reduction, while only 5% of patients in the control group experienced 50% pain reduction. In the Slangen et al. RCT, treatment success was observed in 59% of patients receiving SCS, while success was observed only in 7% of patients receiving BMT ($P < 0.01$).

Conclusions: Based on these three studies, pain is significantly decreased in patients experiencing severe PDPN when treated with spinal cord stimulation compared to best medical therapy. The spinal cord stimulator implantation is a surgical procedure that has risks that patients should be made aware of prior to treatment. However, in patients where benefits outweigh the risks, SCS should be considered a treatment option for severe PDPN.

Key Words: Spinal cord stimulation, painful diabetic peripheral neuropathy, neuropathic pain

INTRODUCTION

Diabetes Mellitus (DM) is a chronic disease that occurs when the body does not make enough insulin or develops a resistance to insulin, leading to elevated blood glucose levels (hyperglycemia).[1] Type 1 diabetes manifests earlier in life, while type 2 manifests later, usually from a lifetime of poor diet and lack of exercise. Uncontrolled diabetes has a variety of complications, including stroke, heart disease, heart attack, and neuropathy. Nerve damage, leading to painful diabetic peripheral neuropathy, may result in patients that have had diabetes for an extended period of time or have had difficulty controlling their blood glucose levels.[1] The exact cause of PDPN is unknown, however researchers believe that diabetic neuropathies are due to a number of factors, including: high blood glucose, abnormal blood fat levels, low insulin, neurovascular factors, nerve inflammation, mechanical injury, genetics, and lifestyle factors. These patients may experience numbness, tingling, burning, weakness, loss of reflexes, loss of coordination, and pain as the nerve damage progresses.[1] This can happen in any area of the body: the arms, legs, digestive tract, and sex organs. The most common type of diabetic neuropathy affects the periphery, which causes symptoms in arms or legs.[1]

It is estimated that a total of 23.1 million people in the US have a diagnosis of diabetes and approximately 7.2 million people have diabetes but remain undiagnosed.[2] These 7.2 million people are likely to have uncontrolled blood glucose levels and are therefore at an increased risk of developing complications of diabetes, like PDPN. It is estimated that 60-70% of patients with diabetes will develop some type of neuropathy.[1]

The CDC estimates that a total of 14.2 million emergency department visits in 2014 had diabetes listed as a diagnosis, including 207,000 visits for hyperglycemia and 245,000 visits for hypoglycemia.[2] In addition, the estimated total direct and indirect cost for diabetes is $245

billion in the US alone. Average medical expenses are approximately 2.3 times higher in patients with diabetes than without.[2] The more complications that exist, the more the cost increases.

The first line treatment of diabetic complications is to gain and maintain control of blood glucose levels through blood glucose monitoring, diet, exercise, and medications that help to decrease blood glucose like Metformin and Insulin.[1] It is also very important that diabetic patients see their primary care physician and have their feet checked regularly. Most diabetic patients have regular appointments every three to six months for blood work, including a Hemoglobin A1c, which measures the average blood glucose level over three months. For PDPN, pain relief can be gained through a variety of medications, including: antidepressants, anticonvulsants, and opioid or opioid like drugs. Duloxetine and Pregabalin are approved by the FDA specifically for treating PDPN.[1] These medications often come with side effects and are not always approved for use in older individuals. Over the counter medications such as ibuprofen and acetaminophen generally do not work well for nerve pain. Lastly, topical treatments, like capsaicin cream and lidocaine, are available and are most commonly applied to the feet. These medications are relatively safe but do not necessarily provide relief.[1]

The above listed treatment options have been found to be the most effective medical options thus far in treating pain associated with PDPN, and therefore are deemed the "best medical therapy" (BMT). However, they are often accompanied by side effects and are not effective enough in relieving pain. Several studies have shown that spinal cord stimulation has been more effective than BMT in treating pain associated with PDPN. The mechanism of action of spinal cord stimulation has not been fully uncovered, but it is thought to be multifactorial.[3] The spinal cord level at which the SCS is placed is dependent on the location of symptoms, but is

generally in the thoracic region. This paper evaluates two randomized controlled trials (RCTs) and one case series that show the efficacy of SCS compared to BMT in treating severe PDPN.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Is spinal cord stimulation an effective therapy to treat severe lower extremity diabetic peripheral neuropathy pain that has lasted over one year and has not responded to medical therapy?

METHODS

Two randomized controlled trials and one case series were used in this review. The population includes men and women over the age of 18 with type 1 or type 2 diabetes mellitus experiencing moderate to severe lower extremity painful diabetic peripheral neuropathy for at least one year that has not been successfully treated by BMT. The intervention used in the two RCTs was SCS along with BMT. The control group received BMT alone. In the case series, the intervention was spinal cord stimulation. All three studies found a significant decrease in pain levels in patients receiving SCS treatment for severe PDPN compared to patients receiving BMT only.

The key words used in searching for the articles addressed in this review included the following: diabetic neuropathy, neuropathic pain, and spinal cord stimulation. All three articles were published in English in peer-reviewed journals. The articles were selected based on relevance to the clinical question and if they addressed outcomes that were patient oriented evidence that matters (POEMs). The inclusion criteria included RCTs and other studies published after 2006. Studies that were excluded were those published before 2006, those that involved patients less than 18 years of age, and those discussing upper extremity or mild PDPN.

Statistics reported included the following: p-value, ABI, RRI, NNT, and NNH. Specific demographics and characteristics of each of the studies are detailed in Table 1 below.

Table 1- Demographics and Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W /D	Interventions
Abd-Elsayed, et al. (2014)[4]	Case Series	3	79, 60, 39	Patients with resistant painful peripheral neuropathy	There were no patients excluded in this study.	0	Implantation of a spinal cord stimulator
De Vos, et al. (2014)[5]	RCT	60	>18 years old	Patients that were evaluated and diagnosed with diabetic neuropathy by a neurologist, had refractory diabetic neuropathic pain in the lower extremities for >1 year, and had an average pain score of >50 on a visual analogue scale (VAS).	Patients with pain due to atherosclerotic lesions, patients with infection, neuropathic pain in upper extremities, coagulation disorders or taking anticoagulant medication, patients with psychiatric disorders, and patients addicted to drugs or alcohol.	6	Implantation of a spinal cord stimulator over the physiologic midline with the tip of the electrode lead between vertebral levels T9 and T12. Medication adjustments and PT were allowed at any time at the discretion of the physician.
Slangen, et al. (2014)[6]	RCT	36	18-80 years old	Patients with moderate to severe PDPN present in the lower limbs, experiencing insufficient pain relief and/or unacceptable side effects with drug treatment, with pain present <12 months, and a mean pain intensity daytime or nighttime of >5 on a NRS.	Patients with neuropathic pain in upper limbs, neuropathy of origin other than DM, recent neuro-modulation therapy, drug or alcohol abuse, blood clotting disorders, immune deficiency, PV disease, active foot ulcers, life expectancy <1 year, pacemakers, local infection, psychiatric disorders, pregnancy, cardiac or pulmonary failure, unstable glucose control, or use of anticoagulants.	2	Implantation of spinal cord stimulator with the lead positioned over the thoracic level and settings tailored to each patient.

OUTCOMES MEASURED

All three studies measured pain, reported by the patients. In the Abd-Elsayed, et al. case series, pain was measured using a visual analogue scale (VAS), from 0-10, with 0 representing no pain and 10 representing maximum pain. Pain was measured at baseline and 1-month post SCS implantation.[4] In the De Vos, et al. RCT, pain was measured using a VAS, from 0-100, with 0 representing no pain and 100 representing the worst pain imaginable. Pain was measured at baseline, 1 month, 3 months, and 6 months. Treatment success was defined as a greater than 50% reduction in pain on the VAS.[5] In the Slangen, et al. RCT, pain was measured using a numeric rating scale (NRS), from 0-10, with 0 representing no pain and 10 representing maximum pain. Pain was measured at baseline, 3 months, and 6 months. Treatment success was defined as a greater than 50% relief of daytime or nighttime pain intensity on the NRS for at least 4 days.[6]

RESULTS

Two RCTs and one case series evaluated the efficacy of spinal cord stimulation as management for painful diabetic peripheral neuropathy. The Abd-Elsayed, et al. case series describes three patients with peripheral neuropathy: 1) a 79-year-old male with bilateral lower extremity painful diabetic peripheral neuropathy for 11 years, 2) a 60-year-old male with HIV-induced neuropathy for 15 years, and 3) a 39-year-old female with neuropathy secondary to chemotherapy for 3 years.[4] These patients had failed best medical therapy and therefore SCS was presented as an option to manage their pain. All three patients experienced a reduction in pain with the one-week trial period of the spinal cord stimulator. Patient 1 and patient 3 elected to receive the permanent SCS implantation and continued to experience pain reduction. Patient 2 did experience pain relief with the SCS trial, however his health declined and he elected to postpone the implantation.[4] The patient most relevant to this study, patient 1, reported improved

VAS scores with the trial and after implantation reported an overall 60% pain reduction. In addition, he reported improved activities of daily living such as walking and grocery shopping, and breakthrough oral pain medications were successfully weaned down.[4] The results are displayed below in Table 2.

Table 2- Abd-Elsayed, et al.[4] VAS scores and pain reduction

Patient	Baseline VAS pain score	VAS score after 1 week of trial SCS	VAS score after implantation	Percent reduction in pain from baseline
1	9/10	3/10	2/10	60%
2	9/10	Not reported	Not reported	95%
3	8/10	Not reported	Not reported	95%

In De Vos, et al., a RCT, a total of 60 patients with an average VAS pain score of at least 50/100 were selected and randomized in a 2:1 fashion to either the SCS with BMT group, or the BMT only group.[5] For all patients in both groups, adjustments in BMT, including medications and physical therapy, were allowed at any time throughout the duration of the study. All patients were followed up at 1 month, 3 months, and 6 months to assess pain on a VAS. Two patients failed to follow up for their 1 month visit and four patients failed to follow up at the 3 month visit. Data analysis was performed regardless. Treatment success was defined as a greater than 50% reduction in pain.[5] After 6 months, the SCS group had a 60% success rate, while the control group had only a 5% success rate ($p < 0.001$), showing a significant difference in treatment effect between groups (Table 3).[5] RBI was calculated to be 11, ABI was calculated to be 0.55, and NNT was calculated to be 2. This is significant because it means that two patients would need to be treated in order for one patient to see a benefit compared to the control. Detailed calculations can be seen in Table 4 below. This study was not without adverse events. A total of six patients withdrew from the study: four from the SCS group and two from the control group. Therefore,

the study contained 36 patients in the SCS group and 18 patients in the BMT group. From the SCS group, one patient could not get the implant, two patients did not get any relief in the trial, and one patient left this study for another. In the control group, two patients withdrew due to unrelated illnesses.[5] In the SCS group; there were two cases of infections, one femur fracture, one cardiac arrest, and four patients that needed repositioning of the SCS device. In the control group, there were two infections, one carotid artery stenosis, one myocardial infarction, one atrial fibrillation episode, and one coronary bypass surgery. All adverse events were treated and resolved during the study period.[5]

Table 3- De Vos, et al.[5] treatment outcomes

	VAS baseline (out of 100)	**VAS 6 months (out of 100)**	**Treatment success**
SCS group	73 (SD=16)	31 (SD= 28)*	60%
Control group	67 (SD=18)	67 (SD=18)**	5%

**P<0.001, significant treatment effect within group*
***P<0.001, significant treatment effect between groups*
SD = standard deviation

Table 4- Calculations for treatment success from De Vos, et al.

		Relative benefit increase (RBI)	**Absolute benefit increase (ABI)**	**Number needed to treat (NNT)**
CER	EER	$\frac{\text{EER- CER}}{\text{CER}}$	EER - CER	1/ABI
0.05	0.60	11	0.55	2

In Slangen, et al., a RCT, 36 patients with severe PDPN not responding to best medical therapy were randomly assigned in a 3:2 fashion to either SCS with BMT or BMT only.[6] Twenty-two patients were assigned to the SCS group, while 14 were assigned to the BMT only group. Patients were followed at 3 months and 6 months. Treatment success was defined as greater than 50% reduction in daytime or nighttime pain for at least four days. At 6 months, treatment success in the SCS grouped was reported in 13 out of 22 patients (59%) and 1 out of 14 (7%) in the control group ($p < 0.009$).[5] In addition, 41% of patients in the SCS group reported

greater than 50% daytime pain relief compared to 0% in the control group ($P < 0.001$), while 36% in the SCS group reported greater than 50% of nighttime pain relief compared to 7% in the control group ($P < 0.01$).[6] These results can be seen in Table 5. RBI was calculated to be 7.43, ABI was calculated to be 0.52, and NNT was calculated to be 2 for treatment success. This is significant because it means that two patients would need to be treated for one patient to see a benefit compared to the control. Detailed calculations are shown in Table 6. Two patients withdrew from the study: one patient in the SCS group contracted an infection six weeks after the implantation and had the SCS removed and another patient suffered from a dural puncture during SCS implantation, subsequently dying from a subdural hematoma.[6] The NNH is 11, which is significant because it means that if 11 patients are exposed to SCS implantation, an average of one more patient will have an adverse event that they would not have had otherwise. Detailed calculations can be seen in Table 7.

Table 5- Slangen, et al.[6] Treatment outcomes

	SCS Group	**Control Group**	**P-Value**
Treatment success	13/22 (59%)	1/14 (7%)	$P < 0.009$*
> 50% reduction on NRS for daytime pain	9/22 (41%)	0/14 (0%)	$P < 0.001$**
> 50% reduction on NRS for nighttime pain	8/22 (36%)	1/14 (7%)	$P < 0.01$***

**P < 0.009, significant treatment effect between groups*
***P<0.001, significant treatment effect between groups*
****P<0.01, significant treatment effect between groups*

Table 6- Calculations for treatment success from Slangen, et al.

		Relative benefit increase (RBI)	**Absolute benefit increase (ABI)**	**Number needed to treat (NNT)**
CER	EER	$\frac{\text{EER- CER}}{\text{CER}}$	EER - CER	1/ABI
0.07	0.59	7.43	0.52	2

Table 7- Calculations for harm from Slangen, et al.

		Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
CER	EER	$\frac{\text{EER- CER}}{\text{CER}}$	EER - CER	1/ARI
0	0.09		0.09	11

DISCUSSION

Diabetes is a very common condition and if uncontrolled can come with an array of complications, including PDPN.[2] While medical treatment is an option, it is not always the safest, not always cost effective, and more importantly for patients it does not always relieve pain. This review evaluates an alternative treatment for painful diabetic peripheral neuropathy: spinal cord stimulation. Each study discussed contains limitations. First, this study was restricted to severe peripheral neuropathic pain that was only located in the lower extremities. Spinal cord stimulation as a treatment for mild neuropathic pain or pain in the upper extremities was not addressed, and the results cannot be generalized. In addition, these studies evaluated spinal cord stimulation for patients that have suffered from pain for a long time, in some cases many years, and these patients have already failed best medical therapy. It is unknown if SCS would be an effective treatment in patients with severe pain that have not tried BMT for as long or do not use BMT in combination with the stimulator. Lastly, in the two RCTs, there have not been published studies following these patients after the final six month follow up. It is unknown if the spinal cord stimulators continued to be effective or if they caused any long-term complications.

Spinal cord stimulators have been studied for a variety of indications, including: failed back surgery syndrome, complex regional pain syndrome, intractable angina, neuropathic pain secondary to HIV, and neuropathic pain secondary to chemotherapy.[3] Caution is recommended in patients with coagulopathy, pacemakers, and certain psychological conditions. An active

systemic or local infection is a contraindication for SCS trial and implantation (aside from HIV), but the implantation can be performed once the infection is cleared.[3]

Studies involving spinal cord stimulators are limited in terms of their concealment and blinding. First, patients receiving BMT only knew that they were not receiving the spinal cord stimulator because it is unethical to undergo a surgical procedure and implant a device that would not be used. Likewise, patients receiving the spinal cord stimulator knew that they were receiving the experimental treatment, because it is unethical to perform a surgery without the patients' knowledge. In the De Vos, et al. RCT, patients in the control group were offered to receive SCS therapy at the conclusion of the study if they desired it.[5]

CONCLUSION

All three studies demonstrated that spinal cord stimulation is an effective alternative treatment for severe painful diabetic peripheral neuropathy in patients over the age of 18 that have failed best medical therapy. The complications of diabetes can be very debilitating and more concrete evidence of an effective treatment is necessary. Further studies should address patients with diabetes that are experiencing other types of neuropathic pain, including upper extremity peripheral neuropathy and more proximal neuropathy that affects the thighs, hips, and buttocks.[1] Patients may also experience autonomic neuropathy affecting the digestive tract, sexual response, the heart, and the lungs.[1] Treatments should be evaluated for all types of neuropathy. Along with this, the safety of a spinal cord stimulator being placed higher on the spine will have to be evaluated. This will allow the stimulator to relieve symptoms along other areas of the body. Despite the range of use that spinal cord stimulation is being evaluated for and the success presented in this review, it is still a fairly new subject that will require expanded research before it can be used as common practice in treating neuropathic pain.

References

1. Nerve Damage (Diabetic Neuropathies). National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/nerve-damage-diabetic-neuropathies. Published November 1, 2013. Accessed October 3, 2017.

2. National Diabetes Statistics Report. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/data/statistics/statistics-report.html. Published July 17, 2017. Accessed October 3, 2017.

3. McKenzie-Brown, A. Spinal cord stimulation: placement and management. Up to Date. https://www.uptodate.com/contents/spinal-cord-stimulation-placement-and-management?source=search_result&search=spinal%20cord%20stimulator&selectedTitle=1~5. Updated November 1, 2016. Accessed November 25, 2017.

4. Abd-Elsayed A, Schiavoni N, Sachdeva H. Efficacy of spinal cord stimulators in treating peripheral neuropathy: A case series. *J Clin Anesth*. 2016;28:74-77. doi: 10.1016/j.jclinane.2015.08.011 [doi].

5. 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(11):2426-2431. doi: 10.1016/j.pain.2014.08.031 [doi].

6. 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(11):3016-3024. doi: 10.2337/dc14-0684 [doi].