

Retrospective Case Series on the Treatment of Painful Diabetic Peripheral Neuropathy With Dorsal Root Ganglion Stimulation

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Background: The dorsal root ganglion (DRG) has been identified as an important neural structure in the development and maintenance of chronic pain. We present a retrospective case series of patients with refractory painful diabetic peripheral neuropathy (PDPN) that underwent electrical stimulation of the DRG and report on changes in their overall perceived pain and complication rates.

Methods: Ten diabetic males (mean age 65.2 [SD 8.8] years) with painful symptoms of the lower limbs were enrolled and trialed with up to four quadripolar percutaneous DRG stimulation leads between L2 and L5 spinal levels. Patients received a fully implantable neurostimulation system (Abbott Laboratories, Sunnyvale, CA, USA) immediately or after a successful trial period (>50% reduction in pain). Overall perceived pain was measured by visual analogue scale (VAS) at baseline, one-week postimplantation and one-, three-, six-, and twelve-month follow-up ($n = 5$).

Results: Ten patients were included in this retrospective study. Seven of these subjects received permanent stimulator implants after successful externalized or intraoperative trials. Two of those patients subsequently required explantation, due to failure to capture primary pain area ($n = 1$) and personal reasons ($n = 1$). For the five subjects that proceeded to clinical follow-ups, baseline VAS was reduced by an average of 63.90% (SD 21.39; $p < 0.001$) postimplantation. For four patients with available 12-month follow-up data, mean relative reduction in overall perceived pain averaged 64.16% (SD 35.8; $p < 0.001$).

Conclusion: Early findings from this small retrospective case series, suggest DRG is a safe and effective neuromodulation modality to improve painful symptoms in PDPN patients. Future prospective trials are required to further investigate the use of DRG stimulation for this clinical indication.

Keywords: Chronic pain, diabetic polyneuropathy, dorsal root ganglion stimulation, lower limb pain, neuromodulation

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INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common and debilitating long-term complication of diabetes mellitus (1). It is typically defined as a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvascular alterations resulting from chronic hyperglycemia exposure and cardiovascular risk covariates (2). While it is possible for DPN to progress asymptotically, epidemiological studies indicate clinical manifestations present in up to 34% of patients as painful diabetic peripheral neuropathy (PDPN) (3,4). Painful symptoms arise as a direct consequence of abnormalities in the peripheral somatosensory system (5).

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These are focal to the toes, feet, legs, hands, and/or arms. Patients often describe the pain as burning, tingling, electric shock-like, or stabbing in nature that is exacerbated at night (6). Pain can also occur in the presence of allodynia and/or hyperalgesia (7). Impaired physical and psychological function is concomitantly reported in this patient population resulting in significantly decreased quality of life and increased anxiety and depression (8). Given the increased morbidity risk associated with PDPN, patient treatment is paramount yet continues to remain suboptimal due to the poor understanding of pathogenesis of pain in PDPN.

Current guidelines recommend pharmacological intervention as first-line treatment of PDPN-related symptoms (9). However, only one third of patients typically achieve clinically significant (>50% reduction) pain relief (10). In patients with severe neuropathic pain that remains refractory to medication, neuromodulation is a safe alternative treatment modality (11).

Several small controlled (12–15) and uncontrolled (16–18) trials have reported significant pain relief following traditional spinal cord stimulation (SCS) in PDPN patients with relatively long-term efficacy (up to 36-months) and little associated morbidity.

While these preliminary findings are encouraging, it is recognized that traditional SCS has limitations, the most prominent being its variability in efficacy; 20–40% of patients remain refractory to the therapy despite optimal lead location and paresthesia coverage (12,19). Furthermore, there is a propensity for SCS-induced paresthesia to lose its clinical effectiveness over time (20). Lead migration within the epidural space (21) and postural changes (22) can produce unpleasant paresthesias. Lastly, targeting pain distributions in distal locations is difficult due to the potential to recruit more superficial neural fibers within the dorsal column (23) and dorsal roots, leading to extraneous stimulation in nonpainful areas. Given the aforementioned clinical issues with traditional SCS, exploring alternative neuromodulation targets that afford greater specificity and efficacy is warranted in this patient population.

With its role in transmitting pain signals from distally extending sensory neurons, the dorsal root ganglion (DRG) has emerged as a promising clinical target for chronic pain management (24,25). A completely reversible procedure with minimal invasiveness to the patient, stimulation of the DRG can provide precise anatomical targeting that is impervious to positional effects (25) in regions conventionally challenging to treat with traditional SCS (i.e., foot, groin, and hands) (26–28). For PDPN patients whose painful symptoms are most predominant in the lower limbs, this level of specificity and efficacy is highly desirable.

A number of small case series and prospective studies in patients with chronic intractable pain of varying etiologies demonstrate implantation of a neuromodulation system (Abbott Laboratories, CA, USA) designed to target the DRG can provide clinically significant pain relief when other conservative treatments have failed (26–29). In the largest, prospective cohort study to date of 32 patients with intractable pain of the low back and/lower limbs (29), DRG stimulation was found at 12-months to reduce perceived pain in the legs and feet by an average of 62% and 80%, respectively. Importantly, paresthesia coverage remained stable through to 12-months postimplantation. More recently, a retrospective review by Schu et al. showed DRG stimulation can provide targeted and sustained pain relief in patients with chronic groin pain, a notoriously difficult anatomical area to treat with neuromodulation (26,27).

To date, no study has explored the potential therapeutic benefit of DRG stimulation in diabetic patients with refractory PDPN. The objective of this work is to present data collected retrospectively from ten patients with PDPN of the lower limbs that underwent

treatment with DRG stimulation and to report on changes in their overall perceived pain as measured by visual analogue scales (VASs) up to 12-months follow-up.

METHODS

Data were obtained through a retrospective chart review at four separate sites in Australia (Queensland, South Australia) and five separate sites in Europe (The Netherlands, Germany, UK, Sweden), from March 2013 to March 2015. Data release authorization was obtained from all patients prior to the inclusion of their data in the present analyses.

All patients were aged 18 years or older, had chronic intractable pain due to diabetic polyneuropathy of the lower limbs for at least six months, were refractory to stable pain medication (minimum 30 days) and/or had failed previous interventions including SCS. Subjects with unstable neurological symptoms, a baseline VAS score of less than 60 mm, who were pregnant or currently had implanted neuromodulation devices were not included.

Patient primary pain area was considered any part of the lower limbs including the, leg, thigh, shin, calf, and foot. Patients were not excluded if they had painful symptoms in upper peripheral regions (i.e., hands, arms).

Implantation Procedure

As previously described in detail (30), under local anesthetic and light sedation, patients were implanted with up to four quadripolar percutaneous DRG stimulation leads. Trial lead placement at the relevant DRG levels was determined by stimulation-induced paresthesia of the patient's primary pain area during intraoperative patient programming. At European sites, all patients were trialed with the fully implantable neurostimulation leads.

Based on the patient's reported level of pain relief following trial lead implantation, the implanting physician determined whether they received the fully implantable DRG neurostimulation system immediately or if a trial period was necessary. During full implantation, leads were connected to a permanent implantable neurostimulator (INS) located subcutaneously in the patient's upper buttock or abdominal region. For the trial period, implanted leads were connected to an external trial neurostimulator (TNS) for up to 30 days. Patients who were judged to have a clinically successful trial received an INS according to standard surgical procedures. For Australia-based patients, trial leads were removed and replaced with permanent leads at the time of full implantation. Postimplantation programming was initiated within 24–72 hours of surgery. Based on patient's feedback, stimulation was programmed for either subperception or paresthesia with patients able to adjust their perceived level of paresthesia using a wireless controller.

Patient's overall perceived pain was evaluated at 1–7 days postimplantation and at one, three, six, and twelve months. During follow-up visits, stimulation parameters were reprogrammed if a patient's primary pain area was not covered. For Australian site patients, as a standard of care, overall perceived pain was assessed using an electronic, touch-screen based 0–100 mm VAS displayed on a computer tablet (Apple, Inc., Cupertino, CA, USA) where 0 mm indicated no pain and 100 mm indicated the worst possible pain; otherwise a paper-based 0–100mm VAS was used.

The primary outcome measure of this case series was change in patient's overall perceived pain at all follow-ups. Secondary outcomes included device complications and procedure-related adverse events. Data is presented as mean (SD) unless otherwise

Table 1. Summary of Patient Demographics, Overall Perceived Pain Before and After DRG Stimulation Trial, and Pain Body Region Distributions at Baseline.

Patient	Age (years)	Baseline VAS	Post-TNS VAS	Post-INS VAS	Primary pain area	Secondary pain area	SCS surgery
01	72	70	10	10	Foot	–	No
02	67	80	10	10	Foot	Calf	No
03	65	70	30	30	Foot	–	No
04	63	65	N/A	35	Thigh	Shin	No
05	58	100	16	57	Foot	–	No
06	69	76	N/A	76	Leg	Foot	No
07	46	93	N/A	N/A	Leg	Foot	Yes
08	58	90	N/A	N/A	Foot	–	No
09	77	60	61	N/A	Foot	Lower leg	No
10	48	92	76	N/A	Foot	Hands	Yes

indicated. A repeated measures analysis of variance (RMANOVA) with Tukey's post hoc pairwise comparisons was used to compare overall perceived pain at all follow-ups from baseline with a significance level set at $p < 0.05$.

RESULTS

Subject Characteristics

Data from 10 male diabetic patients from three separate pain centers, one private hospital and five academic/teaching hospitals were included in this study. Mean age at time of implantation was 62.3 (SD 10.0) years with mean duration of PDPN-related symptoms of 7.0 (SD 3.1) years, ranging from 3 to 11 years ($n = 5$, data not available for others). Two of the ten patients had failed previous traditional SCS therapy. Overall perceived pain averaged 79.6 (SD 13.5) mm at baseline, with the foot being the most common primary pain area reported by patients ($n = 7$; 64%). A summary of individual patient demographics, VAS before and after DRG stimulation, and distribution of pain locations is presented in Table 1.

Trial-to-Permanent Implant Procedures

From March 2013 through to March 2015, ten patients were included in this retrospective case series. Of those, seven (70%) received implanted neurostimulators after experiencing successful

intraoperative testing ($n = 3$) or externalized stimulator trial phase ($n = 4$). The three remaining subjects that did not proceed to permanent implant either failed to achieve adequate pain relief during a trial ($<50\%$ reduction, $n = 2$) or were unable to have leads placed at the appropriate levels ($n = 1$). Of the seven subjects that had stimulators implanted, two had the devices explanted at or before the one week follow-up for either poor painful area coverage ($n = 1$) or for personal reasons ($n = 1$).

Overall, the median trial duration was five days (mean 6.5 [SD 4.4] days; range 3–15 days). For the five remaining subjects who proceeded to the follow-up stage, mean reduction in overall perceived pain was 79% (SD 14).

Lead Placement

Table 2 shows the implant status and spinal location of all implanted neurostimulator leads for the ten patients who underwent TNS and/or INS procedures. All leads were epidurally placed within the neural foramen at lumbar spinal levels ranging from L2 to L5. A median of three leads were implanted per TNS (mean: 2.8 [SD 1.3] leads; range: 1–4 leads) and INS (mean: 3.0 [SD 1.0] leads; range: 2–4 leads) procedure. All permanent leads were placed bilaterally at one or more lumbar spinal levels during full implantation. Some leads were placed bilaterally in a staggered fashion. With the exception of one patient who had four trial leads removed and replaced

Table 2. Lumbar Spinal Placement of DRG Neurostimulator Leads During TNS and/or INS Procedures and Study Follow-Up Status for Ten Subjects From the Retrospective Case Series.

Patient	TNS lead 1	TNS lead 2	TNS lead 3	TNS lead 4	INS lead 1	INS lead 2	INS lead 3	INS lead 4	Study status
01	L4-L	L5-L	L4-R	L5-R	L5-L	L5-R	–	–	TNS success, followed 1 year
02	L3-L	L4-R	L5-L	L5-R	L3-L	L4-R	L5-L	L5-R	TNS success, followed 1 year
03	L4-L	L5-L	L4-R	L5-R	L4-L	L5-L	L4-R	L5-R	TNS success, followed 1 year
04					L2-R	L4-R	L5-R	L5-L	Direct INS, followed 1 year
05	L5-L	L5-R	–	–	L5-L	L5-R	–	–	TNS success, followed 1 year
06					L5-R	–	–		Direct INS fail, unable to capture painful region
07	–	–	–	–					TNS fail, unable to place leads
08					L5-L	L5-R	–	–	Direct INS success, withdrew for personal reasons
09	L5-L	–	–	–					TNS fail, unable to achieve pain relief
10	L5-L	L5-R	–	–					TNS fail, unable to achieve pain relief

INS, permanent implantable neurostimulation; L, lead placement on left side DRG; R, lead placement on right side DRG; TNS, external trial neurostimulation.

Table 3. Patient Individual VAS Scores Across Time.

Patient	Baseline	Post-TNS	Post-INS	One-month	Three-month	Six-month	Twelve-month
1	70	10	10	10	0	0	0
2	80	10	10	10	10	10	10
3	70	30	30	30	30	30	
4	65		35	40	35	35	35
5	100	15.5	57	56	58	63	77
6	76		76				
7	93						
8	90						
9	60	61					
10	92	76					

with two permanent leads, no patient required any trial lead revisions prior to full implantation.

Efficacy: Overall Perceived Pain

RMANOVA yielded statistically significant average improvements in baseline VAS across all follow-up visits ($F = 6.01$; $p = 0.0019$). Baseline VAS was reduced by an average of 48.6 (SD 16.1) mm or 63.90% (SD 21.4; $n = 5$) (Tukey's post hoc test; $p < 0.001$) after permanent implantation. At the six-month follow-up, pain relief was sustained with an average VAS reduction of 49.4 (SD 19.2) mm or 65.6% (SD 27.1; Tukey's post hoc test; $p < 0.001$). Twelve-month follow-up data showed continued pain relief with VAS scores decreasing by an average of 48.3 (SD 25.3) mm or 64.2% (SD 35.8; Tukey's post hoc test; $p < 0.001$). Table 3 and Figure 1 presents the individual and mean VAS scores of patients at baseline ($n = 10$), post-TNS ($n = 6$), post-INS ($n = 6$), and at one-month ($n = 5$), three-month ($n = 5$), six-month ($n = 5$), and twelve-months ($n = 4$) follow-up.

Device Complications and Procedure-Related Adverse Events

Two patients had their INS systems explanted prior to the one-month follow-up visit (29% of retrospective sample implanted). One patient due to personal reasons unrelated to device performance and the other due to failure to capture the primary pain area (left side of lower limb) following single lead revision surgery two-weeks postimplant (due to lead dislodgement). This same patient also experienced a dural puncture at the time of full implantation, resulting in a post-dural-puncture headache that did not require

intervention. No other device complications or procedure-related adverse events were reported.

DISCUSSION

Based on findings from this small retrospective case series, DRG stimulation may be a safe and effective neuromodulation modality to improve painful symptoms in patients with refractory PDPN. Specifically, percutaneous stimulation of the DRG was shown to reduce overall perceived pain in the lower extremities (foot and thigh as primary pain areas) by an average of 64% at the 12-month follow-up visit. Importantly, only one serious adverse event (lead dislodgement) that resulted in the implant system being explanted was reported. While these findings are encouraging, the small number of patients reviewed precludes strong inferences as to the superiority of DRG stimulation over existing treatment modalities. Future prospective, long-term trials are warranted to support the hypothesis generating outcomes presented here.

Recent prospective data supports the safety and efficacy of DRG stimulation in the treatment of chronic, intractable pain of the limbs (29). Several small, retrospective case series also highlight the effectiveness of DRG stimulation in neuropathic pain conditions that are anatomically challenging to treat such as groin (27) and phantom limb pain (31). However, no studies to date have investigated DRG stimulation in patients with PDPN of the lower limbs despite it being a common type of diabetic neuropathy and the most common cause of neuropathic pain (32).

Of the ten subjects included, seven achieved clinically significant pain relief following an initial trial period, resulting in a trial-to-implant success rate of 70%. Of the seven patients who underwent full implantation, three achieved $\geq 50\%$ pain relief at the six-month follow-up, two of whom had a reduction of more than 80%. The proportion of patients with $>50\%$ pain relief at six-month follow-up (30% when divided by total number of enrolled patients; 43% when divided by number of permanently implanted patients) compares with published findings by Slangen et al. in which nine out of 22 PDPN patients (41%) who underwent traditional SCS therapy reported $\geq 50\%$ daytime pain relief at six months (14). Improvements in VAS in this study were also comparable to SCS studies evaluating patients with PDPN (13–18). de Vos et al. demonstrated that after six months of SCS therapy, 60% of patients reported over a 50% pain relief with 40% of those patients reporting over 75% relief in pain.

As noted previously, there are several distinct advantages of targeting the DRG over the dorsal column to treat painful symptoms associated with PDPN. The most prominent being the ability to achieve high concordance of painful areas with minimal extraneous

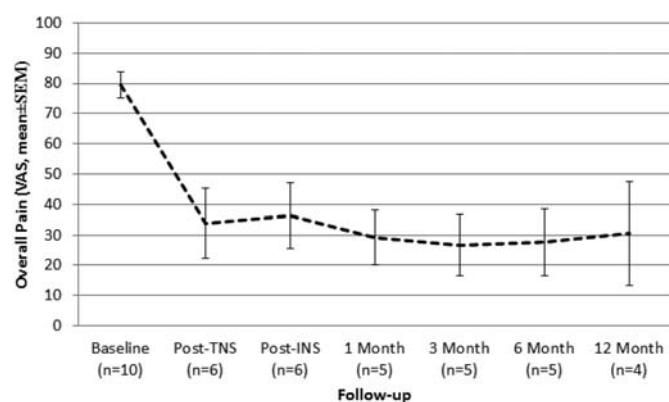


Figure 1. Visual analog scale (VAS) pain ratings were reduced for overall pain. Markers indicate mean VAS $\pm$ SEM. Subject count included is indicated at each follow-up visit. Only successful patients.

stimulation. This has been a major disadvantage of traditional SCS therapy and is overcome through stimulation of primary sensory neurons that directly innervate distal regions and enable subdermatomal coverage. Less cerebrospinal fluid around the DRG also results in a lower amplitude threshold for stimulation, prohibiting the dispersion of energy to other structures in the spinal cord or ventral root (33). Stimulation is also more stable and associated with less positional effects due to the leads being placed near relatively immobile spinal structures (25). These are, however, balanced by a more complex approach to the L4 and L5 foramina where the technique is far more challenging than spinal cord stimulation.

Two adverse events were reported in one patient. One adverse event occurred at the time of full implantation (post-dural-puncture headache) and was deemed to be directly related to the procedure itself. The second serious adverse event (lead dislodgement) was subsequent to full implantation and required the system to be explanted following failure to achieve paresthesia concordance in the patient's primary pain area. Neither of the reported adverse events were anticipated due to the known risks of implantation surgery (21). The approach to L5/S1 interspace dictates an angle of entry that may make dural puncture more possible; care should therefore be taken when performing the dural puncture at this level (34).

While the exact cause of painful symptoms in diabetic patients is yet to be fully elucidated, several metabolic and microvascular systems are thought to be involved. Some of the peripheral and central mechanisms proposed include impaired peripheral nerve blood flow and epineurial shunting (35), increased axonal regeneration and swelling in intraepidermal nerve fibers (36), abnormal somatosensory-evoked potentials within the spinal cord (37), and thalamic neuronal dysfunction (38). Changes in ion channel distribution and expression, sympathetic sprouting, and altered neuropeptide expression (particularly, substance P and CGRP) in the DRG following peripheral nerve injury have also been suggested as causative features (39). It is suggested that electrical stimulation of the DRG enhances pain relief in PDPN patients by both upstream and downstream physiologic effects. Stabilizing the hypersensitivity of DRG neurons that promote spontaneous, ectopic impulse generation as a result of abnormal sodium, potassium, and calcium channel changes and ion fluxes is one such proposed mechanism.

Limitations of our retrospective case series include the small sample size and lack of additional details on the patient population (e.g., diabetes type, changes in medication usage), which precludes us from generalizing the results to the broader PDPN population. Differences in methodology for collection of VAS scores between Australian and European-based patients also restrict the generalizability of the primary outcome with other published studies.

In conclusion, electrical stimulation of the DRG via percutaneous approach may be a safe and effective treatment option to relieve painful symptoms in patients with refractory PDPN of the lower limbs. As this is the first retrospective assessment of DRG stimulation in this patient cohort, with only a small number of cases and limited follow-up, only limited conclusions may be drawn about the long-term safety and efficacy of the therapy, further prospective investigation is warranted to investigate the use of DRG stimulation for this clinical indication.

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Authorship Statements

Drs. Eldabe, Espinet, Wahlstedt, Liem, Patel, Vesper, Kang designed and conducted the study, including patient recruitment and data collection. Dr. Cusack coordinated preparation of the manuscript with important intellectual input from all other authors. All authors approved the final manuscript.

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COMMENTS

This is an excellent article and one of many to come on the topic of DRG stimulation. The most exciting part of this therapy and the expansion of it to new diagnoses. I applaud the authors for completing this publication - the utility of DRG stimulation on DPPN seems logical and many would say this article only proves what most already know. However, this article provides ammunition to gain insurance approval and make sure this therapy is used to its fullest.

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Although it describes a small retrospective case series, this paper is important because it presents the first study of dorsal root ganglion stimulation for painful diabetic neuropathy (PDN). Diabetic neuropathy is by far the most common cause of neuropathic pain and many cases are refractory to analgesic medication. The take home message from the current study is simply that DRGS can in many cases be effective for PDN. As the authors say, we now need RCTs to establish exactly how effective it is.

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Comments not included in the Early View version of this paper.