

Effectiveness and Safety of Dorsal Root Ganglion Stimulation for the Treatment of Chronic Pain: A Pooled Analysis

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Introduction: Since it became available in the mid-2010s, dorsal root ganglion (DRG) stimulation has become part of the armamentarium to treat chronic pain. To date, one randomized controlled trial, and several studies of moderate sample size and various etiologies have been published on this topic. We conducted a pooled analysis to investigate the generalizability of individual studies and to identify differences in outcome between chronic pain etiologic subgroups and/or pain location.

Materials and Methods: One prospective, randomized comparative trial and six prospective, single-arm, observational studies were identified that met pre-defined acceptance criteria. Pain scores and patient-reported outcome (PRO) measures were weighted by study sample sizes and pooled. Safety data are reported in aggregate form.

Results: Our analysis included 217 patients with a permanent implant at 12-month follow-up. Analysis of pooled data showed an overall weighted mean pain score of 3.4, with 63% of patients reporting $\geq 50\%$ pain relief. Effectiveness sub-analyses in CRPS-I, causalgia, and back pain resulted in a mean reduction in pain intensity of 4.9, 4.6, and 3.9 points, respectively. Our pooled analysis showed a pain score for primary affected region ranging from 1.7 (groin) to 3.0 (buttocks) and responder rates of 80% for foot and groin, 75% for leg, and 70% for back. A substantial improvement in all PROs was observed at 12 months. The most commonly reported procedural or device complications were pain at the IPG pocket site, lead fracture, lead migration, and infection.

Conclusions: DRG stimulation is an effective and safe therapy for various etiologies of chronic pain.

Keywords: Causalgia, complex regional pain syndrome type I, dorsal root ganglion stimulation, failed back surgery syndrome, pooled analysis

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INTRODUCTION

Chronic pain is defined as pain persisting past normal healing time, lasting or recurring for more than six months (1). Chronic pain affects approximately 20–30% of the population in the United States and Europe (2,3). It is often a debilitating condition that substantially diminishes quality of life. Post-surgical complications and trauma (25%) and spine problems (20%) are responsible for almost half the incidence of chronic pain (4). Chronic pain has a wide range of etiologies that can be neuropathic, nociceptive, or nociplastic in nature (5,6). Neuropathic pain is caused by a lesion or disease of the somatosensory system. Nociceptive pain arises from harmful stimuli to non-neural tissue and is due to the activation of nociceptors (6). Nociplastic pain is a relatively new term; the International Association for the Study of Pain describes it as “altered nociception despite no clear evidence of actual or

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threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (6).

Spinal nerves, formed from afferent sensory axons (the dorsal root) and motor efferent axons (the ventral root), emerge from the intervertebral neural foramina between adjacent vertebral segments (7). The dorsal root ganglion (DRG) is located at both sides of the spinal cord on the distal end of the dorsal root in the lateral epidural space. The DRG houses the cell bodies of sensory neurons and is an active participant in the development of certain forms of chronic pain (8–13). Because of this, the DRG might be an attractive target for electrical stimulation.

Koopmeiners et al were the first to establish that low-frequency electrical stimulation increases Ca^{2+} influx into DRG neurons, decreases the frequency of multiple action potentials, and significantly reduces conduction velocity (14). A review by Krames summarized various other mechanisms of action of DRG stimulation that have been hypothesized over the years, such as modification of growth factor release, reversal of cytokine release and genetic changes, downregulation of irregular ion channels, and restoration of normal ion flux (15). The end result of electrical stimulation on the DRG neurons is to stabilize and decrease hyperexcitability (15). In addition, to our knowledge, all *in vitro* and *in vivo* animal studies have shown that DRG stimulation has positive effects on pain-related outcomes without causing any inflammation or DRG tissue damage and may actually be anti-inflammatory (16,17).

Conventional spinal cord stimulation (SCS, which applies electrical stimulation to the dorsal column) can result in sub-optimal effectiveness for treating different chronic pain etiologies (18–20). In the last decade, the DRG has become a focus for electrical stimulation with the potential advantage of better target control. The

cerebrospinal fluid layer surrounding the DRG has much lower volume than the one that surrounds the spinal cord. Therefore, lower stimulation amplitudes are required with DRG stimulation compared with SCS, resulting in less postural variation. A recent study with laser-evoked potentials has shown that DRG stimulation might even result in restorative processes by normalizing pain signal transfer from the periphery to supra-spinal levels (21).

We conducted a pooled analysis of published, prospective studies to identify differences in effectiveness of DRG stimulation by pain etiology or location and to investigate the generalizability and reproducibility of individual studies that followed patients for at least 12 months. This pooled analysis evaluates a substantial patient population with complex regional pain syndrome (CRPS). CRPS type I (CRPS-I) is a syndrome characterized by a continuous (spontaneous and/or evoked) pain that is seemingly disproportionate in time or degree to the usual course of pain after trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor edema, and/or trophic findings. A second subtype, causalgia, is a chronic pain condition that can develop after injury or trauma to a peripheral nerve.

This study also set out to give an overview of the DRG stimulation literature, including real-world observations. Finally, pooling the data in analyses may provide a more realistic presentation of outcomes with DRG stimulation therapy.

MATERIALS AND METHODS

A literature search of PubMed was carried out using the search terms "dorsal root ganglion"[All Fields] AND "chronic pain"[All

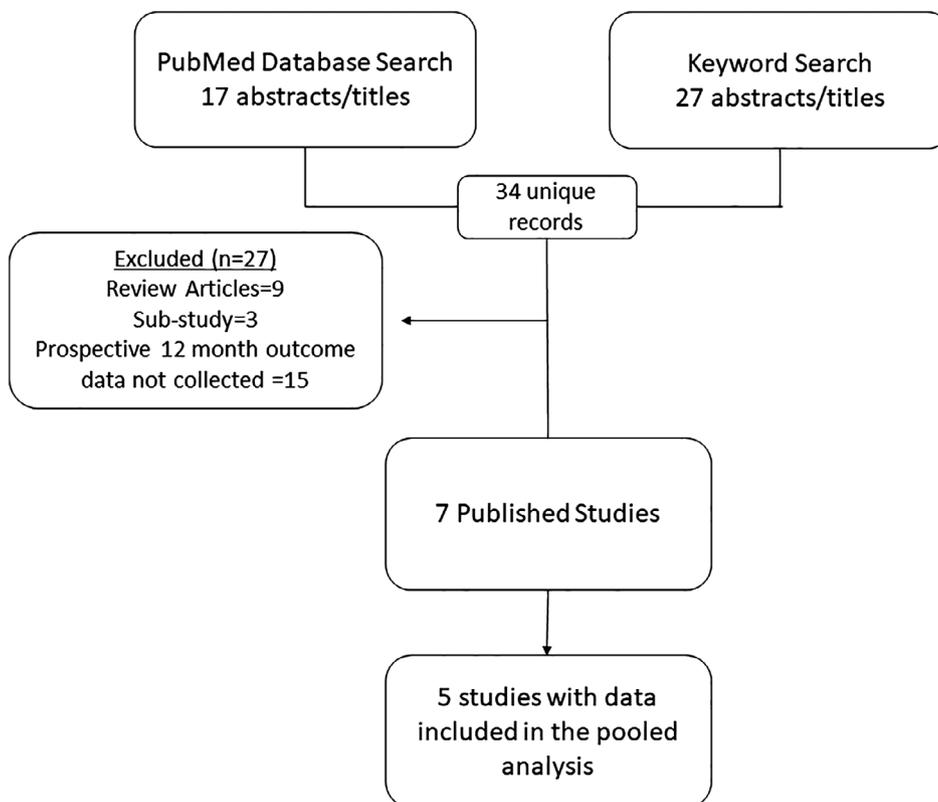


Figure 1. Summary of article selection.

Table 1. Characteristics of All Prospective Studies.

Study	Study design	Age	Sex	Indications	Number of implants	Number of subjects at 12 months	Outcomes
Liem et al.(27)	Prospective, single-arm, observational	54.3 ± 13.3	27 F/24 M	Study total	32	25	Pain (VAS), physical functioning (BPI), quality of life (EQ-5D), mood (POMS), quality and intensity of pain (McGill Pain Questionnaire), paresthesia distribution, patient satisfaction, global impression of change, and safety
				FBSS	8		
				CRPS-I	8		
				Causalgia	6		
				Disc-related pain	4		
				Radicular Pain	2		
Deer et al.(23)	Prospective, controlled, randomized	52.4 ± 12.7	39 F/37 M	Study total	61	55	<i>Primary:</i> treatment success rates for DRG vs SCS
				CRPS-I	30		
				Causalgia	25	25	<i>Secondary:</i> positional effects on paresthesia intensity <i>Non-powered:</i> pain (VAS), quality of life (SF-36), mood (POMS), physical functioning (BPI), patient satisfaction, and safety
Morgalla et al.(28)	Prospective, single-arm, observational	50.4 ± 13.4	13 F/21 M	Causalgia	30	25	Pain (VAS), disability (PDI), catastrophizing (PCS), physical functioning (BPI), depression (BDI), and safety
Morgalla et al.(29)	Prospective, single-arm, observational	56.8 ± 14.4	27 F/35 M	Causalgia	51	40	Pain (VAS), disability (PDI), catastrophizing (PCS), physical functioning (BPI), depression (BDI), and safety
Huygen et al.(24)	Prospective, single-arm, observational	52.0 ± 11.5	42 F/24 M	Study total	56	49	Pain (VAS), physical functioning (BPI), mood (POMS), quality of life (EQ-5D), and safety
				FBSS	25		
				CRPS-I	11		
				Causalgia	15		
				Post-amputation	2		
				Radicular pain	2		
Kallewaard et al.(25)	Prospective, single-arm, observational	47.5 ± 13.4	13 F/7 M	Nonoperated	15	14	Pain (NRS), quality of life (EQ-5D), disability (ODI), mood (POMS), patient satisfaction, and safety
				Discogenic Low back pain			
Kallewaard et al.(26)	Prospective, single-arm, observational	51.0* ± 12.2	7 F/4 M*	Lumbar Discectomy	11	9	Pain (NRS), physical functioning (BPI), quality of life (EQ-5D), disability (ODI), mood (POMS), and safety
Total in seven studies					256	217	

*At permanent implant.

Fields] AND "neuromodulation"[All Fields] AND "prospective"[All Fields]. Google Scholar was also searched using keywords "Dorsal Root ganglion," "neuromodulation," and "chronic pain," Criteria for inclusion were 1) human studies with five or more subjects, 2) studies in an adult population (age ≥ 18 years), and 3) at least 12 months follow-up of prospectively collected clinical outcomes. Articles presenting subgroups or sub-analyses of larger studies were excluded. All studies had to be conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocols and informed consent documentation had to be reviewed and approved by an ethics committee or institutional review board at each site. Written informed consent had to be obtained from patients before initiation of any protocol-specified procedures.

Pain scores collected using visual analog scale (VAS) or numeric rating scale were considered equivalent (22). When collected in

millimeter, a VAS score was converted to centimeter such that all pain scores ranged between 0 and 10. Pain score summary statistics (mean and standard deviation) were provided by the authors of two prospective, independent, physician-initiated studies. We calculated a single pooled mean by weighting the average pain score for each study by sample size. The responder rate within this pooled analysis was defined as ≥50% reduction in pain score.

Patient-reported outcome (PRO) data were extracted from each study and those reported in at least two studies were pooled. Four PROs met these criteria. The EuroQol-5D (EQ-5D index) is a measure of health-related quality of life that measures mobility, self-care, usual activities, pain, and anxiety, and summarizes into one score. The Profile of Mood States (POMS) assesses an individual's transient psychologic state. Brief Pain Inventory (BPI) uses two scales; 1) pain severity and 2) the degree to which pain interferes with function. The Oswestry Disability Index (ODI) assesses

back-related disability. This instrument groups patients by minimal disability ($\leq 20\%$), moderate disability (21%–40%), severe disability (41%–60%), crippled (61%–80%), and bed-bound ($>80\%$). Similar to pain scores, a weighted mean was calculated for each of these instruments. When available, each PRO was compared to the published population normal value and/or minimum clinically important difference (MCID).

Reported device- and procedure-related complications were collated across articles and were reported in aggregated form.

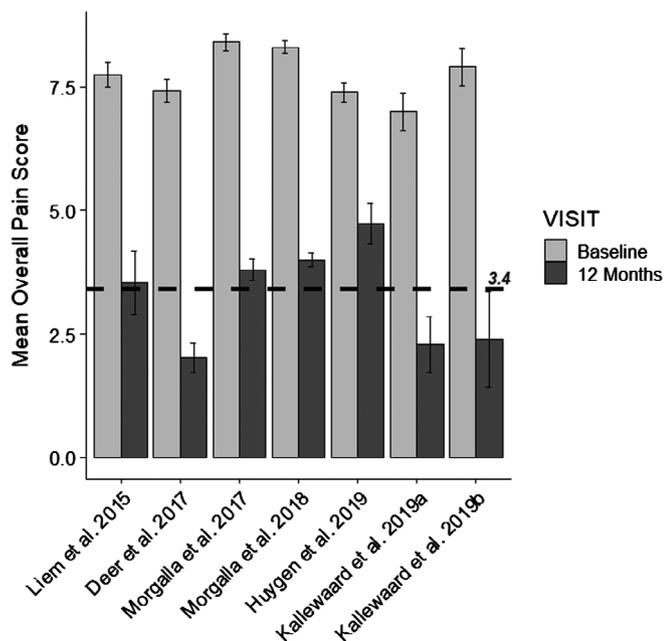


Figure 2. The mean score for each study is shown at baseline and at 12-month follow-up with the standard error of the mean. The mean weighted score across all studies at 12 months (3.4) is shown by a dashed line.

RESULTS

The PubMed Database Search and Google Scholar Keyword Search identified 34 unique records. Of these, 27 were excluded based on the criteria above. Seven prospective studies of independent subject populations were identified; one randomized trial (23), and six prospective, observational studies (24–29). Thus, seven studies were reviewed for this pooled analysis; five were industry-initiated (sponsored by Spinal Modulation [now Abbott, Plano, TX]) (23–27) and two were physician-initiated studies (28,29) (Fig. 1). A total of 256 subjects received a permanent implant. Twelve-month follow-up data were available for 217 subjects (85%). Standard inclusion and exclusion criteria for neuromodulation were applied across all studies. All studies required patients to have persistent pain for at least six months, pain intensity of at least 6 on 0-10 scale, failed conservative treatments, and be physically and psychologically suitable for implantation of a neurostimulator. Patients with unstable pain condition, recent corticosteroid or radiofrequency treatment at the intended site of stimulation, presence of an active implantable device, coagulation disorder or use of anticoagulants, and current/planned pregnancy were excluded. An overview of the design, sample size, age, sex, pain etiologies, and outcome measures for each study is provided in Table 1.

Pooled Analysis of 12-Month Follow-up Subjects

The weighted mean pain score for all patients decreased from 7.8 at baseline to 3.4 at 12 months. Figure 2 presents the mean score for each study at baseline and 12-month follow-up. The most common pain etiologies were causalgia ($N = 104$; 48%), back pain ($N = 53$; 24%), and CRPS-I ($N = 46$; 21%).

Five studies collected data on patients diagnosed with causalgia, either post-trauma or post-surgical nerve damage. Multiple nerves are represented in the data set including the femoral, sciatic, ilioinguinal, peroneal, and tibial. The pooled pain score decreased by 58% (4.6 points) from a weighted mean of 8.0 at baseline to 3.4 at 12 months (Table 2).

Table 2. Pain Score Sub-Analysis in CRPS-I, Causalgia, and FBSS Subjects.

Study	N (at 12 months follow-up)	Overall pain at baseline	Overall pain at 12 months	Responder rates
Causalgia				
Liem et al.(27)	4	7.3 ± 1.0	4.0 ± 3.4	
Deer et al.(23)	25	7.3 ± 2.0	1.9 ± 2.3	
Morgalla et al.(28)	25	8.4 ± 1.0	3.8 ± 1.1	
Morgalla et al.(29)	40	8.3 ± 0.9	4.0 ± 0.82	
Huygen et al.(24)	10	7.0 ± 1.6	4.0 ± 2.5	
	104	8.0 ± 1.2*	3.4 ± 1.5*	68%
CRPS-I				
Liem et al.(27)	7	7.7 ± 1.0	2.7 ± 3.3	
Deer et al.(23)	30	7.6 ± 1.4	2.2 ± 2.3	
Huygen et al.(24)	9	7.8 ± 1.7	5.0 ± 2.8	
	46	7.7 ± 1.4*	2.8 ± 2.6*	71%
FBSS and CLBP				
Liem et al.(27)	8	8.2 ± 0.97	4.8 ± 3.2	
Huygen et al.(24)	22	7.3 ± 2.6	4.5 ± 2.7	
Kallewaard et al.(25)	14	7.0 ± 1.4	2.3 ± 2.1	
Kallewaard et al.(26)	9	7.9 ± 1.1	2.4 ± 2.9	
	53	7.5 ± 1.8*	3.6 ± 2.8*	55%

*Weighted mean and standard deviation.

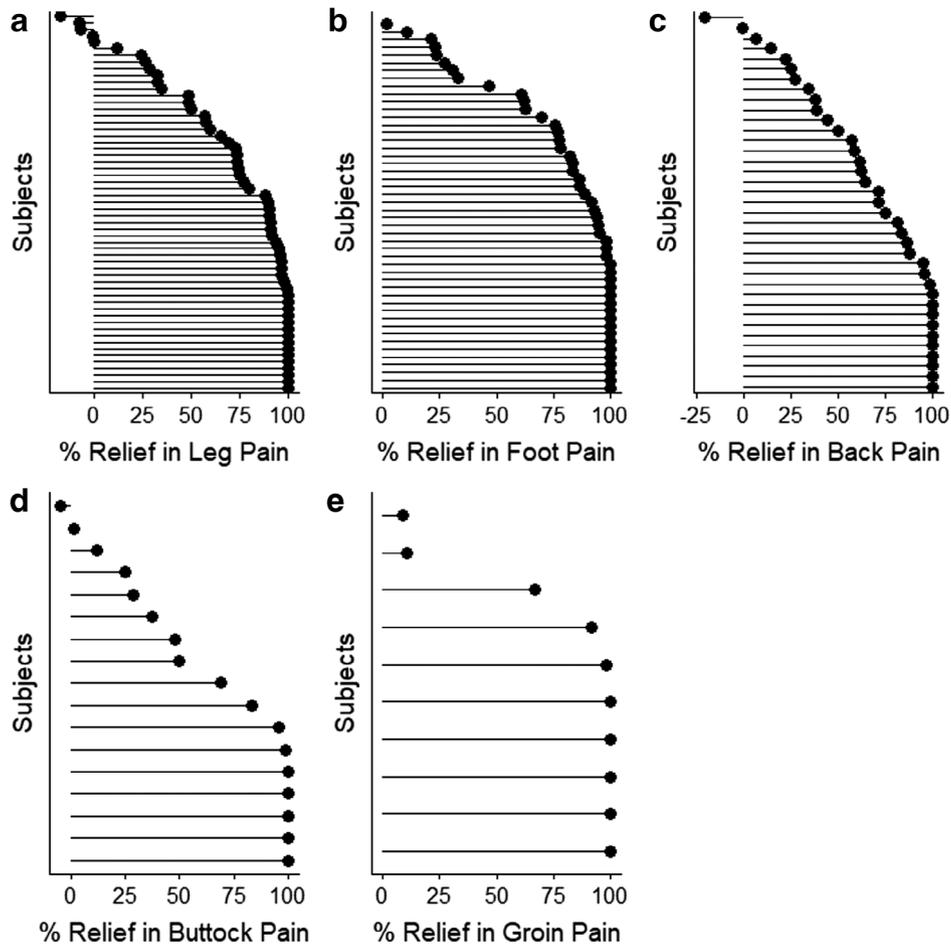


Figure 3. The top five pain locations are shown (A–E) in order of the number of subjects. The line informs the change from baseline and the circle is lined up at the percent relief calculated. Subjects are ordered in increasing order within each panel.

Four studies reported outcomes on DRG stimulation for back pain. The group was heterogeneous and consisted of pain following lumbar discectomy, non-operated discogenic low back pain, and failed back surgery syndrome (FBSS). A total of 53 subjects had 12-month follow-up data available. The weighted average pain score decreased 52% (3.9 points) from a mean of 7.5 at baseline to 3.6 at 12 months (Table 2). Most back pain was reported in combination with foot, groin, buttock, or leg pain ($N = 35$; 66%). Nine patients (17%) had back pain only and two (4%) reported leg pain only.

Outcomes in patients with CRPS-I of the lower extremities were collected in three studies. The weighted average pain score of this patient population decreased by 64% (4.9 points) from a mean of 7.7 at baseline to 2.8 at 12 months (Table 2).

The most frequently reported areas of primary pain were leg ($N = 64$), foot ($N = 50$), back ($N = 37$), buttocks ($N = 18$), and groin ($N = 11$). Pain scores for these discrete regions at 12 months ranged from 1.7 (groin) to 3.0 (buttocks). Responder rates for primary pain areas were 80% for both foot and groin, 75% for leg, 70% for back, and 59% for buttocks. An overview of percentage pain relief per patient for these primary pain areas is shown in Fig. 3. Morgalla et al reported a 73% responder rate at three years for a subset of patients with groin pain (28). A second study from this group collected data from subjects presenting with knee, hand, foot, back, and leg pain and reported an overall 82.5% response rate (29).

Table 3. Patient-Reported Outcomes Common Across Studies Summarized by a Weighted Mean.

Outcome measure	Number of subjects at 12 months	Baseline	12 months
Quality of Life (EQ-5D Index)	90	0.38 ± 0.09	0.69 ± 0.09
Mood (POMS)	97	25.6 ± 14.4	7.3 ± 13.0
Function (BPI: Severity)	138	7.0 ± 1.3	3.9 ± 2.0
Function (BPI: Interference)	138	6.1 ± 3.3	3.3 ± 2.3
Oswestry Disability Index	23	43.8 ± 11.8	17.5 ± 14.4

Four PROs describing quality of life (EQ-5D), mood state (POMS, therapy satisfaction), and physical function (BPI, ODI) were available. Each instrument showed a substantial improvement at the 12-month follow-up visit. EQ-5D index increased from 0.38 to 0.69. Mood disturbance assessed on POMS decreased from 25.6 at baseline to 7.3. As measured on BPI, pain severity decreased by 3.1 points, and pain interference decreased by 2.8. In patients with low back pain, disability reported on ODI reduced from severe disability at baseline (mean score of 43.8) to minimal disability (mean score of 17.5) (Table 3).

All studies reported procedure and device related complications. The most frequently reported complication was pain at the

Table 4. Complications Due to the Device or Procedure in the Pooled Studies.

Complications related to device or procedure	Number of events
Pain at IPG site	26
Lead Fracture	15
Lead Migration	15
Infection	13
Temporary motor stimulation	12
Dural puncture	11
Increased lead impedance	5
Loss of stimulation	2
Buzzing sound in one ear	1
Changes in sensation related to stimulation	1
Disconnection of the external trial stimulator	1
Increased pain after the trial implant procedure	1
Fell due to weakness in one leg	1
Transient motor deficit	1

IPG pocket site ($N = 26$, 10.2%). A total of 15 lead fractures and 15 lead migrations (both 5.9%) were reported. Thirteen infections (5.1%) occurred across studies; seven of which at the IPG site. Additional reported complications were temporary motor stimulation ($N = 12$, 4.7%), all reported in one study, and dural puncture ($N = 11$, 4.3%) (Table 4). Of the 256 permanent implants, a total of 16 (6.3%) were explanted, and were due to infection (8/16), lack of pain relief (5/16), noncompliance (2/16), and by patient request (1/16).

DISCUSSION

The aim of this study was to identify differences in effectiveness of DRG stimulation by pain etiology/or location and to investigate the generalizability and reproducibility of individual prospective studies following patients for 12 months. Our pooled analysis showed high responder rates and effectiveness of DRG neurostimulation for various pain etiologies, mainly CRPS-I, causalgia, and low back pain. These results are consistent with independent, retrospective studies evaluating DRG stimulation in chronic pain conditions such as phantom limb pain, chronic pelvic pain, and groin pain (30–32).

Patients suffering with CRPS-I and causalgia showed a 64% and 58% decrease in pain score at 12-month follow-up, respectively. Effective treatment options in severe CRPS-I are limited, and first-line treatments such as pharmacologic intervention or rehabilitation therapies are often unsuccessful in the long-term, or the evidence is generally absent or unclear (33,34). Kemler et al showed that SCS and physical therapy resulted in pain reduction and health-related quality of life improvement in carefully selected CRPS-I patients up to two years post-permanent implant (35). The reduction in pain intensity was less than 50% (2.1 vs. 4.9) compared to what was obtained for CRPS-I patients in current analysis. The ACCURATE trial showed superiority of DRG over SCS in CRPS-I and causalgia of the lower extremity at 3- and 12-month follow-up (23).

Patients with FBSS ($N = 39$) showed a 3.5-point decrease in overall pain score at 12 months (7.6–4.1). Comparatively, the recent PROMISE trial compared SCS plus optimal medical management (OMM) treatment to OMM only in a FBSS population

(36). In the as-treated analysis, SCS subjects reported a 2.0-point reduction in mean back intensity (7.5–5.4) and a 1.6-point reduction in leg pain intensity (5.2–3.7). The discrepancy in efficacy between our pooled analysis and the PROMISE trial suggests the utility of performing a comparative trial DRG vs. SCS in this patient population.

Two studies in the low back pain group examined more homogenous patient cohorts: pain after lumbar discectomy, and patients with non-operated discogenic back pain (25,26). Recurrent back pain can occur in up to 25% of patients post discectomy within two years (37). Both groups in these studies had high responder rates independent of a surgical intervention; 78% and 79%, respectively. Bilateral L2 placement was used exclusively in the discogenic back pain group and in most patients in the lumbar discectomy cohort. Patients were carefully selected to increase the success of accurate lead placement; those with extensive intra-foraminal fibrosis or epidural adhesions were excluded.

PROs provide information on the impact of treatment on quality of life and physical function from the patient's perspective. One year after implantation, all patients exhibited a substantial improvement in functional outcomes (BPI, ODI), and psychological impact measures as reported on POMS. Patient reported quality of life was within the normal range; the 12 month EQ-5D index was 0.69 compared with population norm of 0.86 ± 0.23 (38). Furthermore, MCID of 0.074 was achieved by 67% of patients (39). Mood disturbance decreased to 7.3, which is below the score of unaffected individuals (12.7) (40). The MCID for BPI subscales pain severity and pain interference were reported as a 2.2- and 2.1-point improvement (41); 58% and 50% of patients met these clinical impact scores, respectively. A clinically meaningful change in ODI (decrease by ≥ 13 points) was achieved by 61% of back pain patients (42). Park et al calculated a MCID of 9-points in patients with pain post-lumbar surgery (43); 83% of this patient population in our analysis met or exceeded MCID. Furthermore, 70% of patients reported an improvement by at least one disability category.

DRG neurostimulation has been shown to effectively treat discrete areas of pain, such as the groin and foot, which are typically more difficult to treat with traditional SCS without causing discomfort in non-painful regions (27,32,44,45). In these specific areas, our pooled analysis showed an 80% responder rate at one year. These results are comparable to other published literature. Morgalla et al reported >70% responder rate for focal (mainly groin and knee) pain at three years (28,29). Moreover, a large retrospective study of 271 patients showed similar pain reduction regardless of focal area being treated (46). The results are consistent with those reported herein; the responder rate across the five most common focal areas treated was 74%. Their analysis also highlighted the importance of obtaining as much coverage over the painful area(s) as possible. This can be achieved by placing additional leads to recruit additional DRGs and authors recommended that a minimum of 2 leads be placed in any DRG stimulation trial (46).

Post-market studies collect real world data, whereas randomized controlled trials are conducted under strict inclusion and exclusion criteria and tightly controlled settings. The only randomized controlled study assessing the efficacy of DRG stimulation to date is the ACCURATE trial (23). This trial showed an overall mean pain score reduction of 69% at 12 months follow-up; 78% of the subjects responded to the therapy compared to a mean pain score reduction of 56% and a 63% responder rate in our pooled analysis. This slightly lower effectiveness in current analysis is not

unexpected, given the addition of post-market data collected in typical clinical settings and heterogeneous patient populations.

The procedural complications reported across the seven studies in our pooled analysis are in line to those observed for other neurostimulation therapies (47). Pain at IPG pocket site was the most commonly complication. A subset of these were due to infection, of which all but one was resolved with antibiotic treatment. However, it is unlikely that all possible complications have been identified in our pooled sample of 256 patients. A recent safety analysis of post-market surveillance data collected from an internal complaint reporting and handling database showed a 3.2% event rate for DRG stimulation devices similar to that reported for SCS in the same time frame (3.1%) (48). The most frequently observed events in this surveillance study are also those identified by our analysis.

Study Limitations

Data of most patients in our analysis come from industry-sponsored studies; there is a need to verify current results in independent studies. Our study was set up to present pooled data up to one-year post-permanent implant as this is the most common follow-up period in published literature. The field is moving toward collecting longer term outcomes as exemplified by recent congress presentations (49–52). These independent studies support effective pain relief and quality of life improvements up to three years post-implant. Future studies should continue to collect longer term outcomes to support a sustained therapeutic effect and ascribe to the initiative on methods, measurement, and pain assessment in clinical trials recommendations (53,54). Furthermore, for a full review of patient experience, additional investigations should be made publicly available such as audits of clinical practice as well as national medical device reporting databases and registries.

Pooling of data has disadvantages as it is difficult to minimize various sources of bias and studies are often heterogeneous. However, eligibility criteria, study design, and follow-up durations were similar across the studies included herein. Although the mean weighted by sample size does not approach meta-analysis methodology, this is the first study to present combined DRG effectiveness of a substantial patient population.

CONCLUSIONS

DRG stimulation is an effective therapy for multiple chronic pain disorders. It is a safe and widely used therapy for patients that have failed to receive pain relief and quality of life improvements from other interventions. With the advent of new stimulation modulations in recent years, it is important that treatments are tailored to specific diagnoses and conditions. The DRG stimulation therapy is most successful for treating focal pain in carefully selected patients.

Authorship Statement

Marie Fahey and Robyn Capobianco designed the study and were involved in drafting/revising the manuscript, data collection, and the statistical analysis. Bram Blomme was involved in drafting/revising the manuscript, data collection, and the statistical analysis. Frank Huygen, Jan Willem Kallewaard, Harold Nijhuis, Liong Liem, Jan Vesper, Matthias Morgalla, and Timothy Deer were involved in data collection, and drafting/revising the manuscript. All authors approved the final manuscript.

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