Scoping Review

Dorsal Root Ganglion Stimulation for the Management of Phantom Limb Pain: A Scoping Review

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Background: Amputees commonly feel an intermittent tingling, piercing, or burning sensation in the region of the missing portion of the amputated limb, a phenomenon known as phantom limb pain. Current treatment modalities include medications, mirror therapy, transcutaneous electrical nerve stimulation, and more recently neuromodulation through spinal cord stimulation and dorsal root ganglion (DRG) stimulation.

Objectives: The aim of this review is to examine the existing literature to identify and analyze evidence for the use of DRG stimulation as a pain relief modality for phantom limb pain.

Study Design: Scoping Review.

Methods: A literature search was conducted using relevant search terms. PubMed, Web of Science, Cochrane, and CINAHL databases were used, and reference lists of selected articles were searched for additional relevant literature.

Results: Most studies analyzed had low to moderate bias in all categories assessed. There are case reports and case series indicating that DRG stimulation could be an effective treatment method for phantom limb pain. Fifteen of 25 patients across 5 studies achieved satisfactory levels of pain relief and significant improvements were reported by all patients evaluated for quality of life. Patient selection and proper targeting of stimulation are important factors in limiting large variability in results while determining effectiveness of this pain relief modality.

Limitations: The studies included in this scoping review are limited by the number of cases and by the length of follow-up. Also, there are no randomized control trials or observational studies with large sample sizes that allow for adequate power. Many of these studies do not have a standardized methodology of quantifying pain relief from DRG stimulation.

Conclusions: The cumulative evidence at present suggests DRG stimulation may be a potentially effective treatment for phantom limb pain, however, a powered prospective randomized controlled trial is needed to assess the long-term benefits of this treatment modality. Given the increasing population of military veterans who are living with limb amputations, finding a modality for adequate long-term pain control is crucial.

Key words: Chronic pain, phantom limb pain, dorsal root ganglion stimulation, neuromodulation, amputation pain, scoping review, phantom limb sensation, neuropathic pain

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Phantom Limb Pain: Over 2.2 million people were projected to live with limb loss in the United States (US) in 2020, with this number increasing to 3.6 million by 2050 (1). Limb loss in US military veterans has increased to more than 1,600 as a result of the conflicts in Iran and Afghanistan post-9/11, with more than 7.4% of major limb injuries requiring amputation (2). Approximately 185,000 limb amputations are performed annually in the United States, a majority of which involve the lower limbs (1).

The most common causes of limb amputation include vascular disease, trauma, and malignancy (1).

Patients with amputations commonly feel an intermittent tingling, piercing, or burning pain in the region of the missing portion of the amputated limb, as if the lost limb is still present. This "phantom" sensation, referred to as phantom limb pain (PLP), is seen in 50%-85% of patients with amputations and often presents within the first 6 months after surgical removal of a limb (3,4). PLP pain encompasses a wide range, from exteroceptive-like to proprioceptive-like pain, and may spontaneously resolve within the first year after amputation (5). Other studies suggest that PLP can also be a persistent condition that stays with the patient for several years after surgical amputation (6,7). Patients with upper extremity amputations and/or the presence of devascularizing trauma are more likely to experience PLP (8). Additionally, women experience a greater average pain intensity (9).

Pathophysiology of PLP

Multiple mechanisms have been proposed for the development of PLP. These mechanisms are multifactorial in nature and can be explained by peripheral or central phenomena, or a combination of both.

Peripheral Mechanism

Nerve injury during amputation can cause neuronal damage, allowing for deafferentation. This leads to inflammation and neuronal overgrowth in the residual limb, which results in upregulation of voltage-sensitive sodium channels, allowing for stump hyperactivity and increased spontaneous afferent input that is then perceived as pain or tingling (8,10).

Central Mechanism

The central mechanism can be thought of as distinct supraspinal and spinal components. In the supraspinal mechanism, the parts of the motor and somatosensory cortex that previously controlled the amputated limb are reorganized and taken over by nearby zones of the cortex (11). The dissociation that occurs causes painful sensations that may be related to the incongruence of motor intention and sensory feedback and a corresponding activation of the parietal and frontal brain areas (8,12).

In the spinal mechanism, deafferentation from a peripheral nerve injury can cause functional changes and loss of afferent input to the dorsal horn of the spinal cord (13). This leads to decreased inhibitory impulses from brainstem reticular areas and increased autonomous activity of dorsal horn neurons described as "sensory epileptic discharges" which are perceived as painful sensations (12).

Dorsal Root Ganglion Mechanism

Amputation causes dorsal root ganglion (DRG) axons to disconnect from distal targets. Injured axons within the residual limb and remaining peripheral nerves generate spontaneous activity from ectopic, hyperexcitable loci, causing aberrant signaling through the spinothalamic tract which is then perceived as PLP (14).

Phantom Limb Pain Treatment Modalities

Currently, there are multiple methods to help treat PLP, with a majority of providers using a multimodal approach. Pharmacotherapy prescribed for PLP includes antidepressants, opioids, antiepileptics, N-methyl-D-aspartate receptor antagonists, and analgesics (15,16). However, randomized, controlled studies with amitriptyline (17,18), gabapentin (19,20), and memantine are conflicting in regard to effects on PLP relief (21). Physical therapies, such as electroconvulsive therapy, repetitive transcranial magnetic stimulation , and transcutaneous electrical nerve stimulation , have shown to markedly reduce pain intensity for short periods of time, but did not have any long-term effects (22,23).

Adjuvant therapies, such as cognitive behavioral therapy, mirror therapy, acupuncture, and biofeedback, have also been utilized (12,24). Regional nerve blocks with lidocaine and/or corticosteroids can result in immediate relief but the duration of this pain relief is highly variable and temporary (12). Peripheral nerve stimulation has also been tried as a treatment for phantom limb pain in the lower extremities, with multiple case studies and a pilot study suggesting favorable results when targeting the sciatic and femoral nerves (25,26). More recently, neuromodulation including spinal cord stimulation (SCS) and DRG stimulation have been used as a treatment option in refractory cases of PLP (24,27).

DRG Stimulation

DRG stimulation is a method of neuromodulation for chronic pain relief. The goal of DRG stimulation is to provide focused pain control to areas such as the hand, foot, or groin (28) that cannot be properly treated with traditional SCS techniques. One or more electrical leads are placed into the epidural space close to the

DRG using fluoroscopic guidance in order to receive input from the painful area (29). An implantable pulse generator is then programmed to provide stimulation based on the pain detected by the 4 electrode contacts on each lead.

Current indications for DRG stimulation include Complex Regional Pain Syndrome (CRPS) Types I and II (30,31). The US Food and Drug Administration approved the use of DRG stimulation for lower extremity CRPS in 2016 (32), though the technique is still being investigated for its long-term outcomes and alternative uses. Other off-label uses that have shown pain relief in patients include thoracic neuralgia resulting from peripheral nerve injury (33), diabetic neuropathy (34,35), neuropathic groin pain (28,36), as well as failed back surgery syndrome (37-39).

Similar to SCS, DRG stimulation may have the possibility of hardware-related complications due to lead migration, but there are unique benefits specific to the use of DRG for pain relief. Studies have shown that DRG stimulation, when compared to SCS, has led to greater improvements in quality of life (30,39), significantly reduced postural variation in paresthesia (30,40), and significantly reduced extraneous stimulation of non-painful areas (30).

The ability of DRG stimulation to target specific areas of pain makes it a promising pain relief modality in patients with amputations who have PLP (30,31). Some even believe that the primary sensory neurons of the DRG are what may be responsible for the pain signals in PLP (41,42). However, others believe that neuroplastic maladaptation in the stump may occur, causing deviation of the pain from the expected pattern and creating variability in predicting lead locations for DRG stimulation (43). Regardless, PLP is similar to other neuropathic pain syndromes for which DRG has shown benefit, and thus may be a prospective avenue of pain management to further investigate.

The purpose of this scoping review was to examine the existing literature to identify published studies that have explored the use of DRG stimulation for PLP in practice and to analyze outcomes from these studies to better understand if there is enough evidence supporting this as a promising pain relief modality for PLP.

Methods

Overview

Our scoping review was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines. This review was not registered and thus a protocol was not prepared.

Literature Search

A systematic search of the PubMed, Cochrane, Web of Science, and CINAHL databases was conducted using the search terms "dorsal root ganglion," "stimulation," "phantom limb pain," "amputation pain," "stump pain," and other variations of these terms, in order to identify all potentially relevant published articles written in English as of March 30, 2020. The complete search syntaxes utilized are provided in the supplementary material (Appendix).

Study Selection

A total of 33 unique publications were identified after removing duplicates (Fig. 1). Two authors independently scanned through these articles using the PRISMA-ScR methodology. We subsequently checked the references in these articles to locate additional relevant publications not identified during the database searches (44). Studies were excluded at the title, abstract, and full text levels and any discrepancies in selections were settled by the third author. Exclusion criteria included nonhuman studies, review articles, and book chapters. Studies were also excluded if they did not report on outcomes after placement of a DRG trial or implant.

Data Extraction

Study characteristics and patient characteristics including patient age, gender, lead location, trial versus permanent DRG stimulator implant, type of amputation, years since amputation, and follow-up period were extracted independently. Outcomes including improvements in quality of life, self-reported percentage of pain relief, and pain intensity measured with the Brief Pain Inventory (BPI), Visual Analog Scale (VAS), or Numeric Rating Scale (NRS-11) were also extracted. The collected data were then cross-checked by another author. The data were then synthesized by analyzing outcomes in individual studies and by pooling data points for self-reported percentage of pain relief.

Discussion

Summary of Existing Studies

Table 1 provides a summary of the 5 studies identified that used DRG stimulation in cases of phantom limb

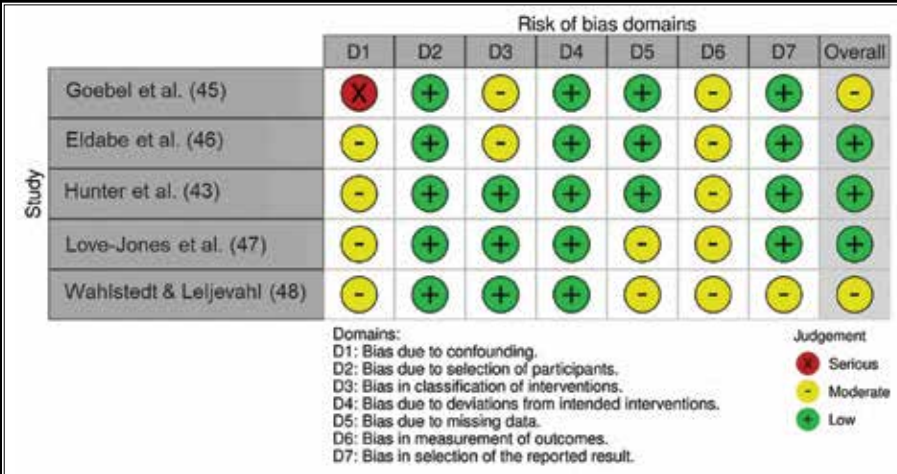

Fig. 1. *PRISMA-ScR flowchart depicting study selection methodology.*

Table 1. *Existing studies utilizing dorsal root ganglion stimulation for treatment of phantom limb pain.*

Author & year	Type of study & journal	# of cases	Lead location	Pain intensity pre-DRG stimulation	Pain intensity post-DRG stimulation	Quality of life improvement	Follow-up (mos)
Goebel et al. 2018 (45)	Case Study Pain Practice	1	L4	BPI: 9	BPI: 5.9	-Sleep duration increased by 3 hours -Stopped use of crutches -Mood Stabilization	17
Eldabe et al. 2015 (46)	Retrospective Case Series Neuromodulation	8	C6-C7 L3-S1	VAS: 83.5 ± 10.5 mm	VAS: 38.9 ± 27.1 mm	EQ-5D index score: score not reported Significant improvement in quality of life (n = 2)	Post-implant: 9.0 ± 6.3
Hunter et al. 2017 (43)	Case Series Neuromodulation	4 (trialed)	L3-L5	NRS-11: #1: 7-8 #2: 6-7 #3: 7-9 #4: 7-8	% decrease #1: 85% #2: 60% #3: 90% #4: 90%	N/A	Until end of trial period (5 to 7 days)
Love-Jones et al. 2015 (47)	Prospective Case Series (conference abstract in Neuromodulation)	16 (implanted), 22 (total trialed)	N/A	VAS: 86.1 ± 10.5 mm (n = 14)	VAS: 37.8 ± 35.4 mm (n = 10)	EQ-5D index score: 0.271 ± 0.288	6
Wahlstedt A & Leljevahl E. 2013 (48)	Retrospective Case Series (conference abstract in Neuromodulation)	2 PLP	N/A	VAS*: 60.9% ± 13.1% (n = 4) *Also includes 1 CRPS & 2 groin pain	VAS*: 64.6% ± 17.7% (n = 3) After one week, phantom hand pain had improved by 100% in the postamputation pain patient.	N/A	1

BPI, brief pain inventory; VAS, visual analog scale; NRS-11, numerical rating scale; EQ-5D, EuroQol-5 Dimension; PLP, phantom limb pain; CRPS, complex regional pain syndrome.

pain. The 5 studies identified consist of case studies and case reports, with a total of 37 patients with PLP who have DRG implants and/or trials. Three studies were full-length manuscripts, with 2 published in the journal *Neuromodulation* and one published in the journal *Pain Practice*. Another 2 studies were presented at conferences with abstracts published in *Neuromodulation*.

In one case study, Goebel et al (45) found benefits from the use of a DRG stimulation trial in stump CRPS that also presented as minimal PLP. Traditional spinal cord stimulation did not achieve coverage for paresthesia or provide adequate pain relief in the stump of a soldier with midtibial amputation. DRG stimulation at the L4 level was able to provide 60% self-reported pain relief over time. Pain, as quantified by the BPI interference score, decreased 34.4% from 9 to 5.9 after DRG stimulation. Quality of life in the patient, in terms of sleep, mood, and independent ability to walk, also improved over the 17-month follow-up period.

Eldabe et al (46) demonstrated at least 50% relief from phantom limb pain with permanent implantation of DRG neuromodulation in 3 out of 8 patients in a case series. There was on average 52.0% ± 31.9% self-reported pain relief, with one patient claiming complete relief from pain after a five-month follow-up period and another reporting no relief at all after one year of follow-up. Pain as quantified by mean VAS score for the 8 patients decreased approximately 53.4%, from 83.5 ± 10.5 mm to 38.9 ± 27.1 mm. A significant improvement in quality of life was seen in 2 out of 2 patients for which this outcome was assessed; there were no complications reported for all 8 patients. Two patients had poor outcomes due to suboptimal lead placement and one reported substantial pain relief lasting only one month before returning to baseline levels.

Hunter et al (43) determined that utilizing radiofrequency could be beneficial in improving the accuracy of DRG stimulation for postamputation pain. In this case series, 4 patients presented with lower extremity phantom limb pain and had on average 81% ± 14% self-reported pain relief one week after DRG stimulator trials, with all 4 patients having at least 60% pain relief. Outcomes regarding improvements in quality of life were not provided.

Love-Jones et al (47) presented a prospective case series with 22 trialed DRG stimulators for patients with PLP, of which 16 moved forward to receive permanent implants. For patients with a permanent implant, pain, as quantified by the VAS, pain scores decreased approximately 56.1% from 86.1 mm ± 10.5 mm (n = 14) to 37.8 mm ± 35.4 mm (n = 10) after a 6-month follow-up period. Of the 10 followed patients, 6 reported pain relief greater than 50%. Three patients who previously also trialed traditional SCS either failed their DRG stimulator trial or reported less than 25% relief. One patient chose to have explantation after 6 months due to inadequate pain relief. Quality of life according to the EuroQol-5 Dimension (EQ-5D) index score was significantly improved.

Wahlstedt and Lehljevahl (48) presented a case series with patients that had PLP, CRPS, or groin pain. Two patients with PLP due to amputations of the foot and hand were included. After one week, the patient with the amputated hand had 100% pain relief and the patient with the amputated foot had 44% pain relief. Outcomes regarding improvements in quality of life were not provided.

Limitations of Current Studies

The aforementioned studies are limited by the number of cases and by the length of follow-up. As of now, there are no randomized controlled trials or observational studies with large enough sample sizes that allow for adequate power. There is only one study (n = 6) (46) with long-term follow-up of greater than 12 months after implantation of the permanent leads. Thus, the long-term effects of the leads on paresthesia are not fully captured by existing literature. Additionally, existing studies lack data on possible subsequent opioid use during DRG stimulation, as well as details on functional improvements as a result of the treatment.

Risk of bias of the 5 studies was assessed using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool (49,50). Most studies had low to moderate bias in all categories assessed (Fig. 2).

Goebel et al (45) utilized DRG stimulation specifically for the recurrence of CRPS in the stump after amputation (45). While this patient had the longest follow-up for implanted DRG stimulation across all 5 studies, this patient was noted to have only minimal phantom limb pain. Thus, improvements observed may not necessarily be attributed to PLP relief alone, but to CRPS as well.

Hunter et al (43) only followed 4 patients until the end of the DRG stimulator trial. Thus, it is unknown how long-term implants would have affected patients' pain scores and overall quality of life.

Love-Jones et al (47) and Wahlstedt and Lehljevahl (48) were conference abstracts with no full-length manuscripts available to review exact methodologies

and detailed results. Wahlstedt and Lehljevahl (48) also included patients with pain etiologies other than PLP in their reporting of mean VAS scores, not allowing for a true evaluation of pain relief using DRG stimulation in only patients with PLP.

Notably, these studies do not have a standardized methodology of determining pain relief from DRG stimulation. Three studies utilized VAS (46-48), while 2 others used NRS-11 or BPI (43,45). Since patients' perceptions of pain are relative to themselves, it is not possible to accurately convert scores to one standardized scale to run a meta-analysis on this data.

There were also limitations in the scoping review process due to taking a more focused, rather than broad, approach to the search for articles. Additionally, 4 databases were scanned for published articles, but unpublished studies or conference posters with abstracts not published online, were unable to be captured for analysis.

Analysis of Data from Existing Studies

There is evidence indicating DRG stimulation has been utilized as a treatment method for phantom limb pain in a limited number of patients. Individual patient data regarding location of amputation and self-reported pain relief are reported in Table 2. Of the 37 patients identified, 25 patients had follow-up for either DRG stimulator trials and/or implants.

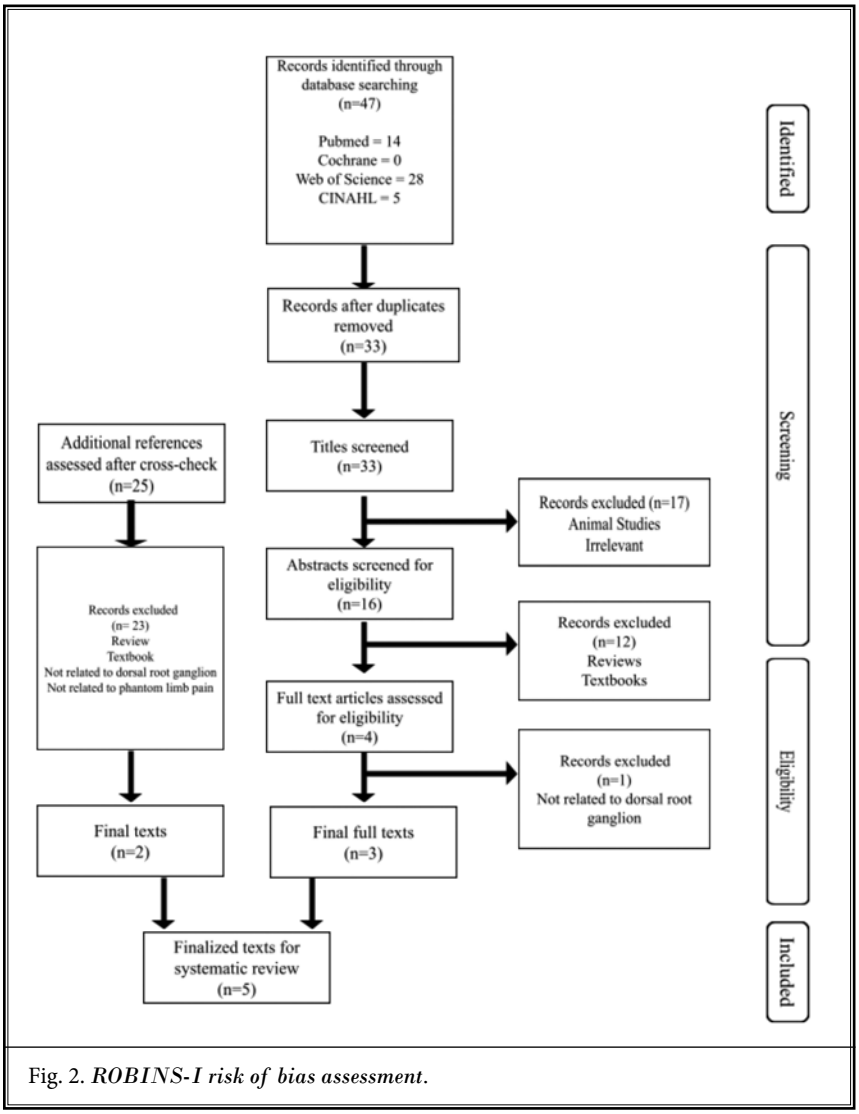

Fig. 2. *ROBINS-I risk of bias assessment.*

Significant improvements in quality of life were reported for all patients for whom these data were collected (n = 9), however, only 8 of those patients had improvement in quality of life as measured utilizing a standardized EQ-5D index score. This score takes into consideration multiple dimensions of life including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression to quantify health status and allow for comparisons (51). Pooled datapoints from 4 studies revealed mean self-reported pain relief of 59.3% ± 31.5 % (n = 14, median 60%). Of all 25 patients with completed follow-up, 15 patients (60%) experienced ≥ 50% self-reported pain relief, the cutoff at which several insurance companies determine the trial to be a success (52,53). All 3 studies reported VAS scores that demonstrated average pain relief ≥ 50% (51-53).

A drawback of utilizing DRG stimulation for PLP is the variability observed in reported outcomes for patients in the 5 studies. Patient selection, as well as proper targeting of stimulation, may have a substantial effect on outcomes, and thus are important factors to consider when determining the effectiveness of this neuromodulatory pain relief modality. Patients with sub-

Table 2. *Individual patient data of those who received dorsal root ganglion stimulation for treatment of phantom limb pain.*

Study	Patient Age	Patient gender	Amputation	Years postamputation	Self-reported pain relief (%)	Follow-up (mos)	Trial vs. implant
Goebel et al. (45)	-	Men	L AKA	2	60	17	Trial
Eldabe et al. (46)	38	Women	L foot	1	28.6	13	Implant
	-	-	L leg	-	50	20	Implant
	28	Women	Above knee	11	-	24	Implant
	-	Men	L foot	6	< 20	24	Implant
	76	Men	Above knee	18	100	5	Implant
	60	Women	R arm	1.5	0	12	Implant
	62	Women	R leg	3	33.3	12	Implant
	35	Women	L arm	15	67.8	5	Implant
Hunter et al. (43)	59	Men	L BKA	14	85	0.25	Trial
	32	Women	R BKA, L AKA	2	60	0.25	Trial
	67	Men	L Syme	18	90	0.25	Trial
	30	Men	L AKA	2	90	0.25	Trial
Love-Jones et al.* (47)							
Wahlstedt A & Leljevahl E. (48)	-	-	hand	-	100	0.25	Implant
	-	-	foot	-	46	1	Implant

* Sixteen permanent implants and 6 additional trials (n = 22) were included in this study, but individual patient data were not provided. Six out of 10 patients followed for the entire 6-month follow-up period reported ≥ 50% pain relief. L, left; R, right; AKA, above knee amputation; BKA, below knee amputation.

optimal lead placement of the permanent implant, after receiving adequate relief from a trial, had less success in achieving sustained pain relief at the end of the follow-up period. The treatment should also only be considered after pharmacological, psychological, or physical treatment modalities have failed or are contraindicated.

Future of DRG for PLP

There is evidence indicating DRG stimulation could be an effective treatment method for PLP. However, there is limited published data on pain relief (n = 25) and improvements in quality of life (n = 9) for patients who underwent DRG stimulation for PLP. There is also limited evidence in the literature to indicate superiority or equivalence of DRG stimulation to traditional SCS.

A more comprehensive, randomized controlled trial with greater power and longer follow-up needs to be conducted. This proposed prospective study should focus on observing the differences in pain relief and quality of life when utilizing DRG stimulation versus an alternative widely accepted pain management modality for PLP, such as traditional SCS. Follow-up for at least one year past implantation of the permanent DRG is needed to be able to assess the long-term effects of neuromodulation. Another potential step toward identifying the effectiveness of DRG stimulation for PLP pain would be to utilize VAS in future case series and prospective studies to allow for a greater pool of data to conduct a meta-analysis. VAS is suggested as it has already been used in 3 of 5 studies identified.

Proper targeting and localization of stimulation are important factors in limiting the variability observed in patient response, as suboptimal lead placement appears to be a major explanation for poor outcomes observed in patients included in the 5 studies analyzed. Future studies should also implement radiofrequency stimulation to identify and map DRG targets before lead placement to allow for better targeting of painful areas to achieve maximum relief (43).

Conclusions

Identification and analysis of the cumulative evidence at present suggests DRG stimulation may be a potentially effective treatment for phantom limb pain, however, more substantive support with a powered prospective randomized controlled trial is needed to assess the long-term effects of this treatment modality. Given the increasing population of military veterans who are living with limb amputations, finding a modality of adequate long-term pain control is crucial (54).

Supplementary material available at www.painphysicianjournal.com

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Search Terms

PubMed search (3-26-2020):

((DRG[MeSH] OR DRG[tiab] OR dorsal root ganglion[MeSH] OR dorsal root ganglion[tiab]) AND (stimulat*[MeSH] OR stimulat*[tiab]) AND (phantom limb pain[MeSH] OR phantom limb pain[tiab] OR PLP[MeSH] OR PLP[tiab] OR amputation pain[MeSH] OR amputation pain[tiab] OR stump pain[MeSH] OR stump pain[tiab]))

Cochrane, Web of Science, and CINAHL search (3-26-2020):

((DRG OR dorsal root ganglion OR dorsal root ganglion) AND (stimulat*) AND (phantom limb pain OR PLP OR amputation pain OR stump pain))