The Efficacy and Safety of Dorsal Root Ganglion Stimulation as a Treatment for Neuropathic Pain: A Literature Review

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Abstract

Objective: Dorsal root ganglion stimulation (DRGS) received its first regulatory approval (CE marking in Europe) in late 2011, and so its use is now almost six years old. Several thousand patients have already been treated, and a landmark trial in lower limb CRPS and causalgia has recently been published.

Methods: In this review we have summarised the literature to date on the use of DRGS in the treatment of neuropathic pain.

Results: The results so far are encouraging, with reports of successful use in treating a wide range of indications including postsurgical pain, CRPS, and phantom pain. Treatment of failed back surgery syndrome (FBSS) appears less successful. The therapy is still young, and long term results are not yet available. There is now good RCT evidence that DRGS provides superior pain relief to spinal cord stimulation for CRPS and causalgia of the lower limb, and produces stimulation that is more posturally stable, with more precise paraesthesia coverage. However evidence of this quality for other indications and pain locations is lacking.

Conclusion: There is now Class A RCT evidence that DRGS provides superior pain relief to SCS for CRPS and causalgia of the lower limb. In the coming years we hope that randomised controlled trials will be performed on an indication-by-indication basis, which, together with the publication of longer term follow up data, will provide a more complete understanding of the role of DRGS in the treatment of neuropathic pain syndromes.

Keywords: Dorsal root ganglion stimulation, neuromodulation, spinal cord stimulation, safety, efficacy

Introduction

The dorsal root ganglion (DRG) houses the somata of primary sensory neurons of all modalities. Excessive firing of some of these neurons due to alterations in gene regulation following injury is a key component of the pathophysiology of neuropathic pain [1], [2]. The mechanisms of this are not fully understood but several ion channel and second messenger systems appear to be involved [3]–[5]. The result of their derangement is that firing thresholds can be dramatically reduced, particularly in Aδ fibres where they may be halved [6], leading to hyperexcitablility and ectopic discharges. The T-junction, where the axon running from the cell soma in the DRG splits into central and peripheral processes, is another site of aberrant activity in neuropathic pain. It normally acts as a low pass filter, limiting the rate at which signals from the periphery can be forwarded centrally, and there is evidence that in peripheral nerve injury and inflammation this filtering mechanism fails, particularly in C fibres, allowing nociceptive signals through at a higher rate.[7], [8].

Electrical stimulation of the DRG can reduce neuronal excitability[9] and the idea that dorsal root ganglion stimulation (DRGS) may be directly treating pathological neurons makes it an alluring target. To date DRGS has been used to treat postherpetic neuralgia [10], phantom limb pain (PLP) [11], failed back surgery syndrome (FBSS) [12], [13] post herniorrhaphy groin pain [13], [14], radicular pain [12], [15], complex regional pain syndrome (CRPS) of the foot [12], [16], knee [17] and distal upper limb [18], postsurgical perineal pain [19], pelvic girdle pain [20], peripheral nerve injury following kidney surgery [13], pain following femoral vascular access [13] and pain following deep vein thrombosis (DVT) [14] amongst other unpublished indications.

DRG leads are sited percutaneously. An introducer sheath containing the lead is passed via a Tuohy needle into the epidural space and fluoroscopically guided into a posterosuperior position in the intervertebral foramen (Figure 1). A trial stimulator may then be attached and the lead tested, with immediate patient feedback. A successful trial may be indicated by relief of pain, reduction of allodynia, and/or adequate coverage with paraesthesia. Once the lead tip is in place in the intervertebral foramen a strain relief loop is deployed in the epidural space to reduce the risk of migration, and the introducer and needle are withdrawn. An implantable pulse generator (IPG) may then be placed subcutaneously and the lead(s) connected to it to complete the system, or the leads may be externalised if an extended ambulatory trial period is desired. Present IPGs can accommodate up to four quadripolar DRGS leads, thus allowing stimulation of up to four DRGs simultaneously, although most commonly only one or two are used. Postoperatively, stimulation is titrated to achieve optimal results and the patient is provided with a remote controller which can be used to modulate the stimulation amplitude [21].

One advantage that is cited for DRGS is the ability to target areas that may be difficult to treat using conventional spinal cord stimulation (SCS) such as the foot and lower back

[15], [21]. Given the location of the stimulator wire on an individual DRG, as one would expect the stimulation is more focussed than with SCS. However it is not strictly dermatomal. In some cases pain-paresthesia overlap can be achieved to a sub-dermatomal degree of precision [21]. Discrete coverage of even a single toe has been reported [23]. This is believed to be due to the combination of a degree of somatotopy which is known to exist in the ganglia [23], and the fact that the same neurons responsible for pain generation are also more sensitive to stimulation, so that appropriately titrated stimulation can affect these alone. Equally, coverage can extend outwards into neighbouring dermatomes, for example allowing treatment of foot pain using an L5 lead only, despite the existence of pain in areas corresponding to L4 and S1.

A well-documented problem with SCS is an inconsistency in paraesthesia across different postures. SCS electrodes are separated from the spinal cord by dura mater and a layer of cerebrospinal fluid (CSF) between the dura and the cord. The thickness of the CSF layer varies with posture due to anteroposterior movement of the cord [24] with the result that both stimulation efficacy and paraesthesia can be different when standing, sitting, or lying [16], [25], [26]. This can be mitigated by providing the patient with different programmes for different postures (and newer IPGs with accelerometers can sense posture allowing automatic switching between programmes) but this considerably increases programming complexity. In contrast, because there is no CSF between the dura and the DRG, DRGS should produce paraesthesia that is posture-independent [16], [21]. The advent of paraesthesia-free variants of SCS is likely to make this a less important issue in the future. It is also often possible to operate DRGS in a paraesthesia free window.

The CSF layer between an SCS electrode and the spinal cord provides an electrical shunt, meaning that much of the current being delivered by an SCS system does not reach the cord [27]. The lack of CSF around the ganglion results in typical DRGS currents in the hundreds of microamperes (μA), whereas SCS currents are measured in milliamperes (mA). DRGS IPGs would therefore be predicted to have a high longevity, but detailed data on battery lifetimes are not yet available.

DRGS received its first regulatory approval (CE marking in Europe) in November 2011, and so its use is now almost six years old. Despite this, several thousand patients have now been treated, and a landmark trial in lower limb CRPS and causalgia has recently been published [16]. The purpose of this review is to summarise the evidence for the efficacy and safety of DRGS as a treatment for neuropathic pain, and to define the major limitations in the evidence to date.

Methods

Literature Search

Two members of the review team searched MEDLINE and Google Scholar for the following phrase: "dorsal root ganglion" AND (stimulation OR modulation) independently to identify relevant titles. The Google Scholar search initially yielded 72,500 results and was therefore refined to article titles only.

Inclusion Criteria

1) Primary research was included provided that it attempted to quantitatively or qualitatively assess the efficacy and/or safety of DRGS in the treatment of neuropathic pain.

2) Study participants must have had a diagnosis of neuropathic pain and have failed appropriate conservative or medical treatment before undergoing surgery.

3) Only complete published manuscripts that had been peer-reviewed were included.

Exclusion Criteria

The following types of study were excluded:

1) Studies performed on animals.

2) Papers not written in the English language.

3) Studies that went on to be re-reported with a longer follow up or included participants who had formed parts of larger cohorts in other studies.

Extraction of Data

Data were extracted and tabulated under the following headings: Author and Year, Study Design, Indication, Participant Number, Demographic, Follow Up, Efficacy Analysis Modalities, Summary of Efficacy Results and Summary of Safety Results.

Data Synthesis

Articles were grouped into the following indications: phantom limb pain, complex regional pain syndrome, failed back surgery syndrome, postherniorrhaphy pain and other indications. The results of the studies were tabulated, and described narratively.

Results

15 papers were found satisfying the inclusion criteria (see table 1). Two of these were excluded for forming part of larger studies [21], [22].

Phantom Limb Pain

Eldabe et al followed 8 cases of phantom limb pain (PLP) treated with DRGS for an average of 14.4 months [11]. Five of these patients achieved pain relief outcomes that were described as good (VAS reduction ranging from 28.6% to 100%). The lack of success in two cases was felt likely to be due to suboptimal lead placement. In one case there was a promising initial result but this was not sustained, possibly due to a delayed dislike of paraesthesia or an initial placebo response. Some of the patients had experienced extreme violence leading to their amputations; it is possible that post-traumatic stress disorder may have influenced outcome in these patients but this is speculative and was not formally tested in the study. Eldabe reports good accuracy of paraesthesia coverage and no complications associated with the surgery.

Complex Regional Pain Syndrome

Garg and Danesh describe a case of CRPS in the distal upper extremity of a 43 year old female who underwent cervical SCS [19]. The patient had scarring at the C5/C6 posterior epidural space, probably as a result of an anterior cervical discectomy and fusion (ACDF) she had undergone over 10 years before. The scar tissue complicated surgery, causing the catheter to exit the C6 foramen and incidentally site the 2 most distal contacts close to the DRG. The patient reported a 70% improvement in pain at one week and the skin in the affected area returned back to its normal colour.

Bussel et al present another successfully treated case of CRPS in a 48 year old woman [18]. They achieved paraesthesia coverage of 90% of the painful area and managed to reduce their patient's pain (measured on a numeric rating scale) from 6-9 to 1-2 over a 3 month follow up period.

Liem at al. present a multicentre prospective case series of patients with various indications for DRGS [12] including 11 patients with CRPS. Patients were fitted with a temporary neurostimulator for a trial period of 3-30 days, and those reporting an improvement in their pain by at least 50% (as measured on a VAS) received a permanent implant. Results were reported at 6 and 12 months [12], [21]. 39 of the total 51 participants, and 8 of the 11 CRPS patients had a successful trial period and were fitted with a permanent implant. Permanently implanted patients reported an average reduction in pain by 74.2% at the end of their trial period whereas the non-responders reported only an average pain relief of 5.0%. The effects of DRGS diminished somewhat over time, but responders reported an average pain relief of 56.3% at 12 months. Results were stratified anatomically rather than grouped by aetiology. Foot pain was most likely to improve (87.5% of subjects achieved at least 50% reduction in VAS at 12 months) and tended to improve more than pain in other sites (79.5% average reduction in VAS for foot pain, compared to 62.4% for leg pain and 41.9% for back pain). Patients were largely satisfied with their treatment, reporting improvements in their quality of life and mood. During two reversal periods where stimulation was stopped the patients' pain returned to near baseline levels.

Seven patients had their devices explanted and were withdrawn from follow up. Two of these patients withdrew from the trial for lack of efficacy. The per protocol analysis used in this study means that attrition bias must be borne in mind when interpreting the data; analysis by intention to treat would probably show a somewhat greater loss of efficacy over time. There were 86 safety events reported across 29 subjects, approximately half deemed to be device related. The most common adverse events (AEs) were temporary motor stimulation (12 incidents), cerebrospinal fluid leak and associated headache (7 incidents), and infection (7 incidents). Two participants received 2 lead revisions each due to high impedance.

The ACCURATE trial [16] is the first randomised controlled trial of DRGS. This study compared DRGS with SCS (the existing standard of care) in patients with CRPS and causalgia of the lower limbs. 152 patients were randomised to receive either DRGS or SCS (76 patients in each group), and a composite primary endpoint was used, defining success as ≥50% pain relief in the primary area of pain after a trial period, and ≥50% pain relief with no stimulation induced neurological deficit three months after implantation. 81.2% of subjects receiving DRGS achieved this endpoint of success compared to 56.7% of those receiving SCS, demonstrating non-inferiority ($p<0.0001$) and superiority ($p=0.0004$) of DRGS. At 3 months the average reduction in VAS in the primary region of pain was 84.1% in the DRGS group and 70.9% in the SCS group. At 12 months the average reduction in VAS in the primary region of pain was 81.4% in the DRGS group and 66.5% in the SCS group. Secondary endpoints were used to assess postural effects on paraesthesia intensity, paraesthesia specificity (i.e. limiting paraesthesia to the target area) and mood. The DRG stimulator showed less postural variation in stimulation intensity consistently over the course of 12 months, higher stimulation specificity and greater improvements in mood disturbance, functional status and quality of life compared to SCS.

There was no statistically significant difference in serious adverse events between the two groups (21 events in 19 subjects, 8 in the DRGS arm and 11 in the SCS arm). Non-serious adverse events were stratified into those which were procedure related, device related and stimulation related. 52 procedure related adverse events were reported in 35 patients in the DRGS arm (46%) and 29 patients in the SCS arm (26%) ($p=0.018$). The most common of these was pain at the incision site, and it was felt that this difference could be due to longer operative times in the DRGS group (average 107.2 minutes) than the SCS group (75.7 minutes). There was no statistically significant difference in the number of device related or stimulation related events.

Failed Back Surgery Syndrome

In a prospective study by Liem et al, of 16 patients with FBSS only 8 (50%) had successful trials and were fitted with a permanent implant [12]. This compares with 69% of the remaining 35 patients in the study group who were having DRGS for other indications. Liem's analysis stratified pain reduction by anatomical site (back, leg, and foot); response rates (defined as at least 50% reduction in pain VAS) for pain in each of these sites were 37.5%, 68.4%, and 87.5% respectively. Pain in FBSS is predominantly in the back and legs, the regions responding least well in this study. The explanation for these results is likely to be that the build-up of epidural scar tissue following failed back surgery makes optimal lead placement difficult, and it may also increase stimulation impedance [28].

Weiner et al [29] describe a case series of 11 patients treated for FBSS with a novel wireless DRGS system. At 6 weeks' follow up 7/11 patients reported at least 50% improvement in VAS. The average pain reduction at 6 weeks was 63%.

The high trial failure rate coupled with relatively low response rates in the body areas concerned suggests that FBSS is not a favourable indication for DRGS. SCS retains a key advantage for this particular indication because the level of electrode insertion is typically well above the level of the previous surgery, so that, unlike with DRGS, the SCS electrode insertion is being done through virgin territory.

Postherniorrhaphy Pain

Schu et al retrospectively reviewed 29 cases of neuropathic pain managed with DRGS, 12 of which were postherniorrhaphy [13]. 25/29 patients including 10/12 with post herniorrhaphy pain had a successful trial of stimulation (trial duration 3-30 days), defined by at least a 50% improvement in their VAS. Between baseline (N=25) and follow up (N=23) pain improved by an average of 71.4%. 19/23 patients had at least a 50% improvement and 11/23 had at least an 80% improvement at final follow up. 13 patients were followed up for 6 months or longer and experienced a mean improvement of 67.5%. 10/13 patients had at least a 50% improvement and 7/13 had at least an 80% improvement at last follow up (42.5 weeks average). Schu et al demonstrate accurate and precise paraesthesia coverage without postural change.

Of the patients with postherniorrhaphy pain the mean VAS reduction was 76.8% with 80% of patients improving more than 50% and 50% of patients improving more than 80%. 5 postherniorrhaphy patients were followed up for 6 months or more with a mean improvement of 74.3%.

Zuidema et al [14] reported on three patients, two of whom had postherniorrhaphy pain, who achieved VAS reductions of 100% and 89% at 3 month and 2 month follow up timepoints respectively. Their third patient was a 46 year old female who had been left with neuropathic pain after a deep vein thrombosis (DVT), and also achieved a drop in VAS score of 89% at 2 months.

Other Indications

Zuidema et al present a case of refractory perineal pain following the excision of a Bartholin's cyst in a 58 year old lady. Stimulation of the S3 DRG and nerve root resulted in a reduction in VAS from 90mm to 10mm in the two weeks following surgery with no IPG or lead related complications [19].

Deer et al performed a prospective case series in which 10 patients, mainly suffering from radiculopathy, were trialled with DRGS for 3-7 days [15]. The average reduction in pain was 70% (n=8), with 6 of 8 patients experiencing at least a 50% reduction in pain. The best improvement was seen in back pain (84%, n=5, whereas foot pain improved 70%, n=3). Participants rated the improvement in their condition as 7 out of 10 while clinicians rated 78% of improvements as a score of 1 or 2 (very much improved or much improved). 78% of patients were able to reduce their analgesic medication during the trial. 17 safety events were recorded in 7 study participants. 3 events were categorised as adverse events (AEs) unrelated to study related activities. The 14 other events, classified as complications, occurred in 6 patients. 12 of these complications were device related and included 7 cases of neurostimulator inactivation (related to a device feature that would halt stimulation after lead impedances changed by a pre-set ratio), a lead migration and a possible reaction to antibiotics. The remaining complications were unspecified.

Rowland et al describe a case of intractable pelvic girdle pain successfully treated with DRGS [20]. The patient was 37 year old female with a 9 year history of chronic pain which had left her heavily medicated and bed bound. Stimulation of the dorsal root ganglia at L1 and L2 afforded her improvements in mobility, a 43% reduction in pain scores measured on a numeric rating scale and a 29% reduction in her McGill Pain Questionnaire score at 6 months.

Discussion

Efficacy

From the literature it is apparent that DRGS can work well for neuropathic pain of several different aetiologies. Liem et al had a successful trial rate of 39/51 (76%), and in the ACCURATE study 61/73 subjects were trialled successfully (84%). The variability in response between patients is also described in SCS [30] and remains largely unexplained. Suboptimal lead placement, unrealistic patient expectations, a subjective dislike of paraesthesia and psychological factors could all contribute to unsuccessful trials in certain individuals.

Different locations or aetiologies of neuropathic pain might be more amenable to DRGS, as is the case with SCS [30]. Liem et al achieved better outcomes in patients with neuropathic foot pain (79.5% decrease in VAS) than patients with back pain (41.9% decrease) [12]. In our experience it is particularly challenging to site DRGS leads in patients who have undergone previous back surgery, probably as a consequence of scarring in the area, and we would not now regard DRGS as a first line option in FBSS.

According to our review initial responders can expect variable degrees of pain relief, on occasion extending up to 100% [11], [14], but consistently averaging 70-80% [10], [12], [13], [15]–[19]. An important trend in the literature is for pain relief to decrease over time [11], [12] and the extent of this might be underappreciated due to attrition bias [12], [13]. This trend is not unexpected and has already been described in SCS [31]–[33]. Fibrotic scars accumulate around SCS leads [34]–[36] and have the potential to reduce current reaching its target [28]. Lead migration may also play a part in some cases. Interestingly the ACCURATE trial [16] reports consistent improvement in VAS scores relating to the primary region of pain over a 12 month follow up (84.1% at 3 months, 81.4% at 12 months), but a reduction in pain relief in the lower limb overall after 12 months (80.9% at 3 months, 69.4% at 12 months).

The ACCURATE trial [16] is the first to directly compare the safety and efficacy of DRGS and SCS. It demonstrated non-inferiority and superiority of DRGS to SCS at a high degree of statistical significance across a number of outcome measures including pain relief, postural stability, paraesthesia precision and mood improvement. The study is limited however to patients with CRPS and we are yet to see whether these results can be replicated in other conditions. The efficacy of DRGS for CRPS looks favourable compared to SCS, but since DRGS is still in its infancy there is currently more high quality evidence to support the use of SCS [37].

Safety

Deer et al [15] report 17 events in 7 patients: 3 adverse events involving transient increases in pain after the procedure, and 14 complications including device inactivation, lead migration and a possible antibiotic reaction. Liem et al report 86 safety events in 29 patients, approximately half related to the device; these included temporary motor stimulation, cerebrospinal fluid leaks, infection, lead migration and lead fracture [12].

The ACCURATE trial is the only study directly comparing the safety of DRGS with SCS. There was no statistically significant difference in serious adverse events, non-serious device related or non-serious stimulation related events between the two groups. Subjects in the DRGS group experienced a higher rate of procedure related adverse events (46.1%) than those in the SCS group (26.3%) ($p=0.018$). The most common of these was pain at the incision site. One explanation for this difference might be longer operative times in the DRGS group (average

107.2) than the SCS group (75.7 minutes). It is noteworthy that in the ACCURATE trial the implanters were experienced in SCS, but performing their first few DRGS cases, and this may partly account for the increased operative time for DRGS.

Complications of DRGS might relate to the operator, the hardware or the patients. With regard to the operator, DRGS is a relatively new technique with an associated learning curve. It is more technically demanding than that of SCS, since epidural access is only the first (and usually most straightforward) part of the procedure, and as yet only a minority of neuromodulators will have developed the optimum skill set for this procedure. Hardware design has already changed once; the initial lead tip design required improvement to facilitate easier removal of a malfunctioning lead, and the design is likely to be refined further with time. Finally, operator experience will better inform patient selection; a good example of this already is the move away from using DRGS in FBSS.

Study design

One cannot overstate the importance of carefully controlling studies into pain management. The placebo effect of surgery has been well documented [38]–[41], and there is some evidence to suggest that medical devices may augment this placebo effect [42]. Whilst it is not possible to blind studies of DRGS because of the paraesthesia that frequently (although not always) accompanies pain relief, non-blinded randomised controlled trials (RCTs) are perfectly possible. This may be in the form of a comparison against existing neuromodulation options (most likely to be spinal cord stimulation or peripheral field stimulation) or against standard medical management. The ACCURATE trial is the first, and to date the only, randomised controlled trial of DRGS.

Conclusion

We have summarised the current literature on the use of DRGS in the treatment of neuropathic pain. The results so far are encouraging, with reports of successful use in treating a wide range of indications including postsurgical pain, CRPS, and phantom pain. Treatment of FBSS appears less successful. The therapy is still young, and long term results and cost effectiveness data are not yet available.

There is now Class A RCT evidence that DRGS provides superior pain relief to SCS for CRPS and causalgia of the lower limb, and produces stimulation that is more posturally stable, with more precise paraesthesia coverage. However evidence of this quality for other indications and pain locations is lacking. In the coming years we hope that randomised controlled trials will be performed on an indication-by-indication basis, which, together with the publication of longer term follow up data, will provide a more complete understanding of the role of DRGS in the treatment of neuropathic pain syndromes.

Authorship Statements

Conrad Harrison performed the literature search and wrote the article. Sarah Epton performed the literature search. Stana Bojanic and Alexander L. Green offered comments and corrections. James FitzGerald served in a supervisory role and offered comments and corrections. All authors approved the final manuscript.

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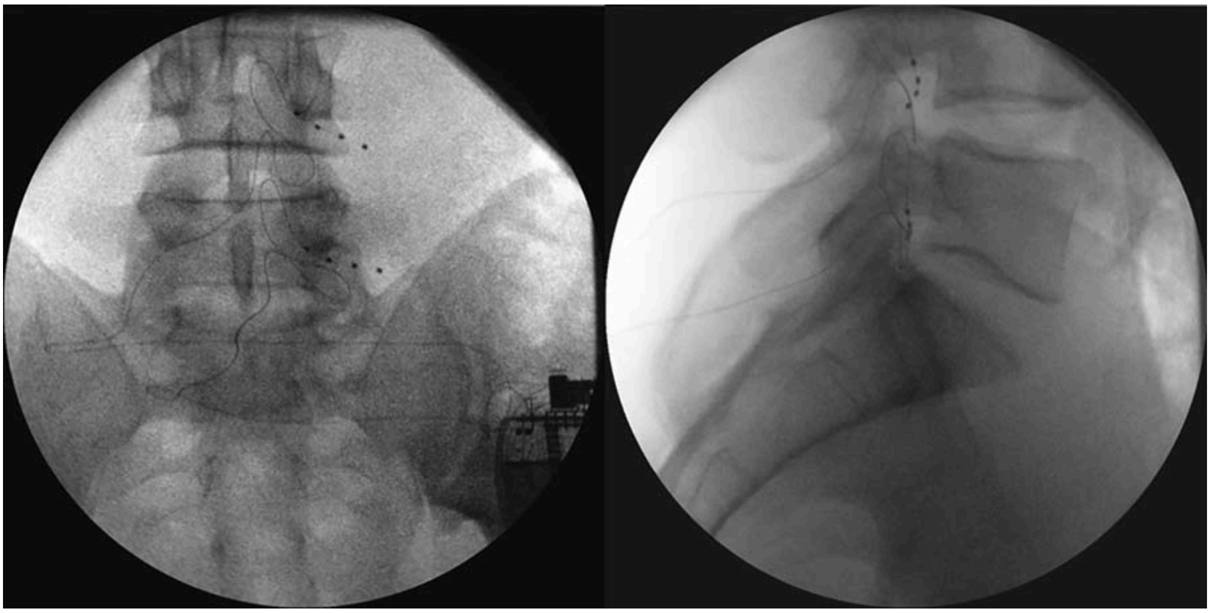

Figure 1. AP and lateral fluoroscopic images showing DRG stimulator wires at L4 and L5. The wires are posterosuperiorly placed within the foramen and strain relief loops have been placed in the epidural space to minimize risk of displacement.