Clinical evidence for dorsal root ganglion stimulation in the treatment of chronic neuropathic pain. A review

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The presence/absence of a control group, and outcomes (pain scores, medications, follow-up, complications).

RESULTS

In 2013, Deer et al. reported data from a pilot study for the ACCURATE study (NCT01923285), sponsored by Spinal Modulation, Inc., Menlo Park, CA, USA and whose results are not to be expected before 2018 (12). Four centres participated and included 10 patients in one arm (5 men/5 women, average age 46 ± 5 years). Six had radicular pain and four other types of neuropathic pain (one diabetic, one post-herpetic, and two non-specified origin). These pains were refractory to a well-led treatment and stable for at least 30 days. The electrodes for DRG stimulation were implanted percutaneously, similarly to posterior cord stimulation. The study did not include a control group. The primary endpoints were the reduction of mean pain score (visual analogic scale, VAS) and the proportion of patients with more than 30% reduction of pain. Patients were followed-up for three to seven
days. The authors reported an average of 70% reduction in pain scores and 80% (8/10) of patients with more than 30% pain reduction. Fourteen complications were reported, including transient increase of pain associated with probes (n = 3), migration of a probe (n = 1), antibiotic reaction (n = 1) and inactivation of the stimulation due to changes of the system impedance (n = 7). Two complications were not further described. Limitations of this study include its very small sample size, open-label design, lack of detailed description of the patients (e.g. concurrent medications) and very short follow-up period.

The same year, Liem et al. reported the data of two independent, prospective, open label, single-arm observational studies sponsored by Spinal Modulation, Inc., one conducted in Europe (3 sites) and one in Australia (4 sites) (13). The identical inclusion, exclusion and judgment criteria for both samples allowed the authors to regroup both studies into one. Fifty-one patients were included, all suffering from neuropathic pain in the trunk, limbs or sacral region resistant to other treatment modalities, lasting a minimum of 6 months. Those 51 patients were implanted with temporary electrodes connected to an external neurostimulator. Thirty-nine had a positive test period (3 to 30 days, pain reduction greater than 50% according to VAS). Out of those 39 patients considered for an internal stimulator, 32 patients were effectively implanted (2 showed lack of compliance, 2 refused implantation and 3 were explanted for infection). Patients were followed up for six months. At two time points, stimulation was turned off for one week and these two periods were used as a control group. The primary end-point of this study was to evaluate the safety (adverse event rate) and feasibility (paraesthesia generation) of the DRG stimulation technique with the Axium neurostimulator. A total of 70 complications were reported, 9 of which were deemed severe: “3 infections affecting 3 patients, one hygroma, one paraesthesias loss, one prolonged hospitalization, one inflammation, one transient cessation of stimulation and one ataxia”. The secondary objective was to assess efficacy, including pain relief and improvement in quality of life, mood and physical functioning. At six months follow-up, the authors report more than 50% pain reduction for over 50% patients as well as improvements on most other secondary measures.

In a second paper, the same team described the follow up of the same sample after 12 months (14). Over this period, a total of 86 adverse events were reported, approximately half of which were deemed related with the device. Among those, the most severe were twelve temporary motor stimulations, seven infections and seven cerebrospinal fluid leaks with associated headache. Four lead revisions needed to be completed and there was also one lead fracture. One implantable generator revision was also performed and a total of seven patients had their device explanted for various reasons (infections, lack of efficacy or lack of compliance with study procedures). After twelve months, the authors reported the same improvement on pain, mood and quality of life as previously described after 6 months. Limitations of this study include its relatively small sample size, one-arm design without real control group and lack of description of the patient population (e.g. duration of the pain syndrome, concurrent medication...).

In a separate paper, Van Buyten et al. reported on the specific use of DRG stimulation on the subgroup of patients suffering from Complex Regional Pain Syndrome (CRPS) patients (15). CRPS diagnosis was based on standard (Budapest) criteria but no details were provided on the stage of the disease. Patients were part of the larger prospective study previously described (14). Out of the eleven subjects trialled, eight reported over 50% pain relief and were subsequently implanted with a permanent neurostimulator. One patient was explanted after one month due to insufficient pain relief. Twelve months later, six patients still felt pain relief greater than 50%. Average pain intensity and pain interference were significantly reduced, while mood and quality of life were improved. Three patients also reported neurovascular changes or improvement mobility. Eleven adverse effects were reported, of which three were deemed severe and three definitely related to the device. In the discussion, the authors compared these results with SCS stimulation. While pain relief obtained was similar, advantages of DRG stimulation included less lead migration, a better ability to achieve pain-paraesthesia overlap and a stability of the stimulation regardless of body position. Limitations of this study include its very small sample size, one-arm design and lack of details concerning the patients (e.g. stage of the disease or concurrent medication).

In a second substudy, Kramer et al. tried to demonstrate the stability of the DRG stimulation across body positions. At each time-point, all patients were asked to report paraesthesia intensity both in supine and upright position, while stimulation programming was kept constant. Both paraesthesia intensity scores and location were similar between these two body positions and over time (16).
**Sc hu et al.** retrospectively reviewed the data from 29 patients suffering from neuropathic groin pain from 11 European institutions (private, academic and teaching hospitals), whose condition was not improved by usual treatments (17). Twenty-five patients had an improvement in their pain symptoms after a test period with external stimulation from 3 to 30 days and were implanted with an internal stimulator. Twenty-three patients were followed up for a median of 26 weeks (0-68 weeks) and reported a 65 to 75% decrease in pain, with over 80% of patients describing a reduction of their symptoms by more than 50%. There was no follow-up data available for one patient and one other patient had his stimulator removed. A subgroup of patients (n = 13) had a follow-up of 6 months or more, with results similar to the entire series. In their conclusion the authors highlighted the accuracy and stability of DRG stimulation but possible complications related to treatment were neither reported nor discussed. The retrospective nature of this study and the lack of detailed information on the patient population are other limitations of this study.

**Discussion**

The six papers included in this review clearly demonstrate the feasibility of DRG stimulation as a treatment option for neuropathic pain. However, they cannot demonstrate either its safety (the number of patients included is too small) or its long-term efficacy (lack of control group, mostly short follow-up with a variable length limiting the analysis in many cases to the qualitative level). It should be noted that Spinal Modulation, Inc. sponsored all the available studies, which could result in conflicts of interest. However, it is the only company that currently is proposing a device for DRG stimulation.

To improve the level of proof, larger randomized controlled trials are needed. Of course, we acknowledge that creating a placebo-controlled neurostimulation study with a blinded control group is very challenging, if not impossible. Moreover, realizing that chronic pain is difficult to evaluate, we agree with those who suggest that the use of psychological and functional assessment and tools such as laser-evoked potentials (LEPs) and quantitative sensory testing (QST) may be important, first to understand symptoms and then to determine which type of population may benefit the most from treatments such as neuromodulation (18).

While further research is needed and only a trial comparing the two stimulation sites could provide a definitive answer, existing studies nevertheless suggest some possible advantages of DRG stimulation compared to SCS. First, it is well demonstrated that eliciting paraesthesia in certain areas of the body (e.g. the groin or one extremities) is difficult with SCS and that this can be a cause of failure (19). The scope of this problem however, may vary depending the team’s experience. While it is not proven at this stage that DRG stimulation provides a definite advantage, it seems that achieving pain-paraesthesia overlap is easier with DRG stimulation, as described by Van Buyten et al. and Shi et al. (15, 17). A second proposed advantage of the DRG stimulation is the consistency of effect, irrespective of the position of the patient, as highlighted by the paper by Kramer et al. (16). With SCS, the quality of the stimulation may vary depending on the position of the subject, even though the precise influence of this phenomenon on the analgesic effect has never been formally demonstrated. While one could consider that this advantage results only in improved patients’ comfort rather than a superior analgesic effect per se, the difficulty for the patient to adapt to the variations in perceived stimulation intensity can also be a cause of failure of SCS. Thirdly, DRG stimulation requires lower current amplitude than SCS to elicit paraesthesia, which in turn could enhance battery life of the implanted neurostimulator (16). Finally, lead migration rates seem to be lower, which could limit the number of surgeries for lead replacement (15). On the other hand, there could be a risk of increased technical difficulties and complications related to the multiplication of electrodes.

All these possible benefits suggest some specific indications for DRG stimulation. These could include: localized pain after surgery (for example orthopedic surgery or groin surgery), post-thoracotomy chronic pain, failed back surgery syndrome, isolated radiculopathy requiring a very precise location of paraesthesia, highly mobile patients seeking constant stimulation and cognitive impairments preventing the rapid adaptation of stimulation intensities in case of change in position.

In conclusion, based on the most recent literature, we consider DRG stimulation a promising technique for the treatment of chronic neuropathic pain. Current evidence however does not yet support its widespread use outside a research protocol and larger trials are needed to improve the level of proof. Study designs should ideally be randomized controlled trials and include well-described populations, long enough follow-up and thorough description of concurrent treatments (pharmacologic and patient integration in a multidisciplinary approach).
References