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A Study on Dorsal Root Ganglion Stimulation in the Treatment of Chronic Neuropathic Pain

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Abstract

Dorsal root ganglion stimulation modulates a central structure in the pathophysiology of neuropathic pain. It has been proven to be superior to spinal cord stimulation for certain conditions and has revolutionized the field of neuromodulation. The access to this technique, however, was restricted for patients with unfavorable anatomy, pain in upper extremities, previous failed neuromodulative procedures or preference for general anesthesia. Little was known about the programming of stimulation parameters in this new setting. Dorsal root ganglion stimulation was performed for the first time with an open implantation technique in patients with challenging anatomical barriers. The percutaneous technique was performed in cervical and high-thoracic segments, as well as in patients with failed SCS, and the outcomes are reported. The experience with preoperative periradicular infiltration therapy in patients operated under general anesthesia is documented in a prospective study to evaluate its impact on clinical outcomes, the first randomized double-blind clinical trial testing different stimulation frequencies is reported.

The open placement of leads for dorsal root ganglion stimulation occurred in patients with foraminal stenosis, strain relief loops and fibrin glue represented an adequate solution for lead fixation and no lead dislocations were seen. Neuromodulation of cervical and high-thoracic dorsal root ganglions with modified technique enabled the treatment of pain etiologies restricted to these spinal segments, clinical outcomes were similar to those commonly achieved in lower extremities. Dorsal root ganglion stimulation represented an adequate add-on therapy for patients who failed spinal cord stimulation alone. The use of periradicular infiltration therapy as preoperative standard changes in many cases the level of intended stimulation trial chosen on anatomical basis. Lower stimulation frequencies down to 20 Hz reduced pain intensity with statistical significance. These innovations and new concepts in dorsal root ganglion stimulation increase the utilization and the efficacy of neuromodulation in patients with chronic neuropathic pain.

Zusammenfassung

Die Spinalganglienstimulation moduliert eine zentrale Struktur in der Physiopathologie des chronischen neuropathischen Schmerzes. Diese Technik ist der Rückenmarkstimulation in bestimmten Erkrankungen überlegen. Der Zugang zur Spinalganglienstimulation war aber erschwert für Patienten mit schwieriger Anatomie, Schmerz an oberen Extremitäten, Versagen anderer neuromodulativer Eingriffe oder Vorliebe für Vollnarkose. Es gab auch wenig Erfahrung mit der Programmierung der Stimulationsparameter. Die Spinalganglienstimulation wurde bei Patienten mit herausfordernden anatomischen Barrieren zum ersten Mal mit offener Implantationstechnik durchgeführt. Die perkutane Implantationstechnik wurde sowohl in zervikalen und hochthorakalen Segmenten als auch bei Patienten mit Versagen der Rückenmarkstimulation durchgeführt. Die Erfahrung mit präoperativer periradikulärer Injektion bei in Vollnarkose operierten Patienten wird in einer prospektiven Studie dokumentiert, die erste randomisierte doppelblinde klinische Studie zu den Effekten verschiedener Stimulationsfrequenzen wird berichtet.

Die offene Elektrodenimplantation in die Spinalganglien erfolgte bei Patienten mit foraminaler Stenose. Zugentlastungsschlaufen und Fibrinkleber waren geeignete Lösungen für die Fixierung der Elektrode. Die modifizierte Technik zur Stimulation der zervikalen und hochthorakalen Spinalganglien erlaubte die Behandlung von Ätiologien, die fast ausschließlich in diesen Segmenten auftreten, und die klinischen Ergebnisse waren ähnlich wie für die unteren Extremitäten. Spinalganglienstimulation war eine adäquate zusätzliche Therapie bei Verlagen der alleinigen Rückenmarkstimulation. Die präoperative periradikuläre Injektion als Standard modifizierte in vielen Fällen die beabsichtigten Höhen für den Stimulationstrial. Niedrige Stimulationsfrequenzen bis 20 Hz reduzierten die Schmerzintensität mit statistischer Signifikanz. Diese Innovationen und neuen Konzepte in Spinalganglienstimulation verbreiten die Anwendung und optimieren die Ergebnisse der Neuromodulation bei Patientin mit chronischem neuropathischem Schmerz.

Abbreviations

BDI	Beck Depression Inventory
CE	*Communauté européenne*
CRPS	Complex regional pain syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
DN4	*Douleur neuropathique en 4 Questions*
DRG	Dorsal root ganglion
DRG-S	Dorsal root ganglion stimulation
DRKS	German Clinical Trials Register
EQ-5D	EuroQuol 5-dimensional
FBSS	Failed back surgery syndrome
FDA	Food and Drug Administration
Hz	Hertz
IASP	International Association for the Study of Pain
IPG	Implantable pulse generator
IRB	Institutional board review
mA	Milliampere
MPQ	McGill Pain Questionnaire
µs	Microsecond
PRT	Periradicular infiltration therapy
RF	Radiofrequency
SCS	Spinal cord stimulation
SD	Standard deviation
VAS	Visual analog scale

Index

1 Introduction

1.1 Chronic neuropathic pain

The International Association for the Study of Pain (IASP) defines neuropathic pain as the result of lesions involving the somatosensory nervous system leading to increased pain sensitivity or spontaneous pain (Scholz et al., 2019). The pain becomes chronic when it lasts for more than 3 months, the prevalence of neuropathic pain in its chronic form was estimated to lie between 6.9% and 10% in the general population (van Hecke et al., 2014). Classic symptoms of neuropathic pain are burning sensation, electric shock-type pain, tingling, numbness, itching, sensation of pins and needles, pain to cold or heat, hypoesthesia to touch or prick, allodynia. Diagnostic tools like *Douleur neuropathique en 4 Questions* (DN4) and PainDETECT assess these characteristics and provide scores correlating to the probability of neuropathic pain component. For the diagnosis of neuropathic pain, the painful area must correspond neuroanatomically to the lesion of nervous tissue.

IASP classifies chronic neuropathic pain in peripheric and central. Causes of chronic peripheral neuropathic pain are (1) trigeminal neuralgia, (2) chronic neuropathic pain after peripheral nerve injury, (3) painful polyneuropathy, (4) postherpetic neuralgia and (5) painful radiculopathy. Chronic central neuropathic pain may be (1) associated with spinal cord injury, (2) associated with brain injury, (3) associated with multiple sclerosis and (4) post-stroke pain (Scholz et al., 2019).

The first-line treatments for neuropathic pain include antidepressants, calcium channel α2-δ ligands and opioid agonists. Antidepressants may include tricyclic drugs like nortriptyline or desipramine, which have anticholinergic side-effects, or selective norepinephrine and serotonin reuptake inhibitors, such as duloxetine and venlafaxine. Gabapentin and pregabalin are calcium channel ligands very commonly used. Opioid agonists like morphine, oxycodone and tramadol have a well-known side-effects profile but are needed in many cases

(Baron et al., 2010). Despite best pharmacological treatment, some patients are refractory. In these cases, neuromodulation is considered as the next step.

1.2 Neuromodulation for chronic pain

Modern neuromodulation started when Shealy used spinal cord stimulation (SCS) for the first time to treat pain (Shealy et al., 1967b, 1967a). Since then, SCS evolved and became the most common neuromodulation technique for the treatment of chronic pain. It consists of an epidural lead with multiple contacts that stimulate the entry zone of the dorsal roots. The lead is connected to an implantable pulse generator (IPG), which delivers regularly electric discharges.

The principles of electrical stimulation are common to all neuromodulative techniques. Electrodes of the stimulation lead are selected to function as cathode and anode. The number and the position of cathodes and anodes influences the shape of the stimulation field. A depolarization area emerges around the cathodes and the anodes form the area of influence around it. Electric discharges are delivered in pulses. The amplitude of each pulse is the value of current and is measured in milliamperes (mA). Increasing the amplitude increases the stimulation field. The duration of each pulse is called pulse width, measured in microseconds (μs). Increases in pulse width lead to a larger depolarization zone with constant stimulation field. Finally, stimulation frequency corresponds to the amount of pulses per second and is indicated in Hertz (Hz). Pulses delivered at a regular rate are known as tonic stimulation, common to all neuromodulation techniques. In SCS there are other waveforms in use, such as burst stimulation, which delivers small packets of few pulses at regular intervals intending to mimic natural firing patterns in the brain. These newer waveforms are not in use for many of the other techniques in neuromodulation.

Other surgical procedures were later developed for the treatment of chronic pain. Motor cortex stimulation was described by Tsubokawa and is used for the treatment of central and trigeminal pain (Tsubokawa et al., 1993). Deep brain stimulation addressed chronic pain before it started being used for

movement disorders (Hosobuchi et al., 1973; Mazars et al., 1974). Peripheral nerves can be directly stimulated (Petersen and Slavin, 2014), intrathecal morphine or ziconotide delivery systems belong as well to the neuromodulation armamentarium (Deer et al., 2019b). The most recent development in surgical pain therapy, however, targeted a structure that makes the interface between peripheric and central nervous system, enabling the transmission of sensory impulses to the spine: the dorsal root ganglion (DRG).

1.3 Dorsal root ganglion stimulation

The dorsal root ganglion is a bilateral neural structure present at every vertebral level. It contains the nuclei of sensory pseudounipolar neurons (Leijnse and D'Herde, 2016). The DRG is still an intradural structure, but it has only a thin surrounding layer of highly conductive cerebrospinal fluid (Brierley, 1950). It is consistently present under the vertebral pedicles in thoracic and lumbar levels (Hasegawa et al., 1996). All sort of sensitive fibers passes through the DRG to get to the spinal cord: myelinated Aβ and Aδ fibers, carrying information from nociceptors, cutaneous mechanoreceptors and from free nerve endings of touch and pressure, and unmyelinated C fibers responsible for temperature and pain.

The DRG plays an important role in the development of neuropathic pain (Krames, 2014). Following a nerve injury, a series of genetic and inflammatory changes occur in the DRG with resulting hyperexcitability (Liem et al., 2016), ectopic firing in Aβ fibers of DRG neurons is an important driver of neuropathic pain (Devor, 2009). While SCS targets mostly Aβ fibers of the dorsal columns, stimulation of the DRG addresses Aβ, Aδ and C fibers and acts in the structure responsible for the maintenance of neuropathic pain.

Therapies targeting the DRG included ganglionectomy, continuous radiofrequency for ablation and pulsed radiofrequency for temporary lesion (Pope et al., 2013). The first report of dorsal root ganglion stimulation, understood as stimulation of nerve roots, was published in 1982 (Blume et al., 1982). Lynch et al. shared the anecdotal and successful experience of stimulating the C2 DRG with an epidural SCS lead for the treatment of postherpetic neuralgia (Lynch et

al., 2011). The first report of modern dorsal root ganglion stimulation (DRG-S) was published in 2013 by Deer et al. Leads were inserted next to the DRG, externalized and connected to an external stimulator. Ten patients with chronic pain were tested for three to seven days and achieved significant pain reduction (Deer et al., 2013).

The first step after the selection of patients that could potentially benefit from DRG-S is the identification of the target level. This can be done either anatomically or with a complementary test, such as stimulation with radiofrequency (Hunter et al., 2017) or periradicular infiltration (Sievert et al., 2021). The implantation procedure may be done under local or general anesthesia. Local anesthesia allows intraoperative testing to confirm the target level. Patients are positioned prone, the procedure is done under fluoroscopy. The puncture is made with a 14-gauge Tuohy needle one or two vertebral levels below the target at the contralateral side. The tip of the needle should pass through the ligamentum flavum and enter the epidural space in the midline, below the spinous process (Figure 1). Confirmation of epidural position is done with a loss-of-resistance test, inserting a guidewire also confirms the correct location (Vancamp et al., 2017).

The lead for DRG-S has four sequential electrodes in the last 20mm of its tip. It has a central canal with a metallic stylet, so that the surgeon can control the movement of the tip. The lead is inserted in the Tuohy needle together with a sheath that provides the curvature needed to achieve the neuroforamen. There are two kinds of sheath, with a big and with a small curvature. For less traumatic insertion, the tip of the lead should be slightly outside the sheath. The sheath has a luer lock capable of locking the lead inside. The assembly of locked lead and sheath is inserted to the desired neuroforamen, the lead is unlocked and the sheath is slightly retrieved leaving the lead in the foramen and showing the four electrodes (Vancamp et al., 2017). The lead should ideally lie superodorsal to the DRG, anterior positions may stimulate the motor root. Lead position is not determinant for outcomes, but superodorsal position demands less stimulator output power (Martin et al., 2020). Position inside the foramen is confirmed with

a lateral fluoroscopic view. With all electrodes outside the sheath, intraoperative testing can be done in patients under local anesthesia.

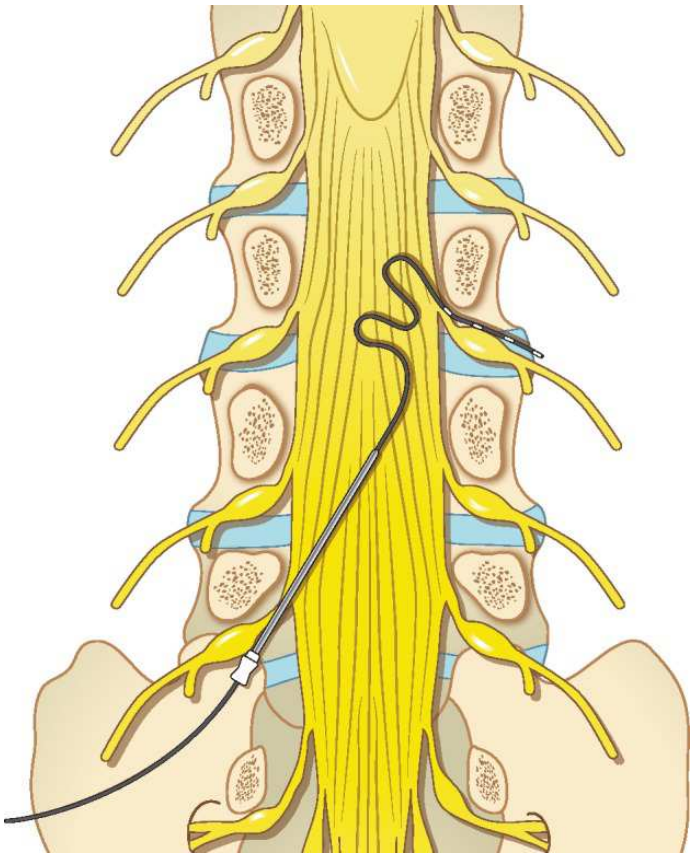

Fig. 1: A DRG-S lead implanted in L3 right neuroforamen superior to the DRG. The sheath was retrieved and two strain relief curves were made in the epidural space. These curves as displayed in the figure are currently not seen as ideal anymore because of higher rates of lead dislocation. Today, S-shaped strain relief loops are preferred. This figure is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs license (http://creativecommons.org/licenses/by-nc-nd/4.0/), no changes were made (Esposito et al., 2019).

The needle is turned away from the foramen and the lead is further inserted to the epidural space to form a strain relief curve that stabilizes the position. The sheath is completely removed leaving the needle in place. The metallic stylet is also removed (Figure 2). The lead is anchored to the fascia and, in the case of a stimulation trial, connected to an extension (Vancamp et al., 2017). The extension will be externalized and connected to an external stimulator. If the patient experiences a significant pain relief, the IPG is implanted

in a second step. Patients submitted to an all-in-one procedure will have the IPG directly implanted.

DRG-S uses frequencies of 4-80 Hz, pulse widths of 40-1000 µs and amplitudes up to 6 mA. Currently, tonic stimulation is the only possible waveform option. Programming starts with stimulation eliciting paresthesia to identify the paresthesia threshold and to evaluate the coverage of the painful area. At the end, patients may be programmed with constant paresthesia or the amplitude may be reduced to a subthreshold level.

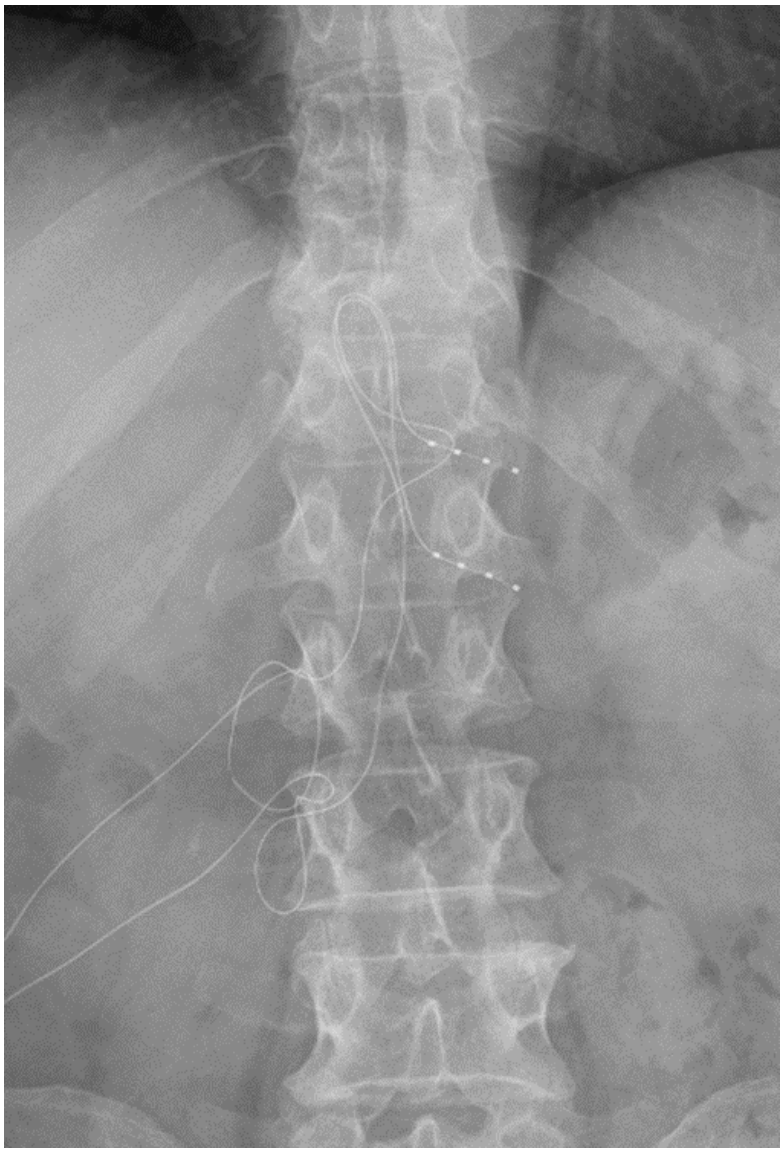

Fig. 2: DRG leads implanted in Th12 and L1 on the left side, the patient suffered from chronic pain after a salpingectomy. This figure is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), no changes were made (Sievert et al., 2021).

Implantation of a definitive stimulation system was first described in another prospective study that documented sustained pain relief for six months. Additionally, adequate coverage of discrete painful areas and stability of paresthesia intensity despite body movements were reported in this study (Liem et al., 2013). DRG-S was extensively performed in Europe, where the only commercially available system was approved in 2011, and in Australia, since approval was given in 2013. Many reports were later published attesting the success of DRG-S in the treatment of pain in the feet (Liem et al., 2015) and in the groin (Liem and Mekhail, 2016), phantom limb pain in lower extremities (Eldabe et al., 2015), perineal pain (Zuidema et al., 2016).

The landmark study that led to FDA approval in the United States was the pivotal, multicenter, randomized clinical trial ACCURATE (A Safety and Effectiveness Trial of Spinal Cord Stimulation of the Dorsal Root Ganglion for Chronic Lower Limb Pain). It compared DRG-S with tonic SCS for the treatment of complex regional pain syndrome (CRPS) and causalgia in the lower extremities. A total of 152 subjects were included, after the stimulation trial the DRG-S arm had 61 patients and the SCS arm had 54 patients with definitive stimulation systems implanted. Patients under DRG-S achieved ≥50% pain relief in 81.2% of the cases vs. 55,7% in the SCS arm at 3 months ($p < 0.001$). At 12 months, 74.2% of the DRG-S patients achieved this endpoint vs. 53.0% of the patients under SCS ($p < 0.001$). Patients of the DRG-S arm also demonstrated significant improvements in quality of life and psychological disposition. They reported significantly less postural variation of paresthesia and less stimulation of nonpainful areas. At 12 months, SCS patients were 7.1 more likely to report paresthesia in nonpainful areas than in the DRG-S arm (Deer et al., 2017). After this study, the FDA approved DRG-S for the treatment of chronic pain associated with CRPS and/or peripheral causalgia in the groin and lower limb in 2016.

DRG-S is interestingly paresthesia-independent. A sub-analysis of the ACCURATE trial showed that 38.3% of the DRG-S arm was paresthesia-free at 12 months, there was no difference in pain relief comparing to patients with paresthesia (Mekhail et al., 2020a). This finding was confirmed in other cohorts,

achieving proportions as high as 87% of paresthesia-free patients (Verrills et al., 2019).

DRG-S targets the painful area in with much more anatomical specificity. The stimulation target has a definite influenced dermatome, while stimulation of the dorsal columns in SCS leads to more diffuse paresthesia areas. Coverage of distal limbs with SCS is usually only possible with the stimulation of multiple dermatomes (Kumar et al., 2011). In a sub-analysis of the ACCURATE trial, the percentage of unrequired paresthesia was only 20% of the painful boy surface under DRG-S comparing to 210% in the SCS arm. The finding is also partially explained by the elevated number of paresthesia-free patients under DRG-S (31.7% vs. 8.8%) (Deer et al., 2019a). Comparing to SCS, DRG-S uses much less energy because the lead is much closer to nervous tissue as a consequence of the very thin layer of cerebrospinal fluid surrounding the DRG. In the case of epidural SCS leads, the delivered energy shunts by the cerebrospinal fluid. In the ACCURATE trial, mean amplitude remained around 3 mA for the SCS arm and never achieved 1 mA for the DRG-S arm (Deer et al., 2017). As the thickness of the layer of cerebrospinal fluid changes with spine movements, the paresthesia and the pain relief elicited by conventional SCS are more variable – a problem that has been recently addressed by the advent of closed-loop SCS (Mekhail et al., 2020b). In contrast, the lead for DRG-S is inserted in the neuroforamen and stabilized by vertebral bone and ligaments.

DRG-S developed very fast as a good option for the treatment of neuropathic pain in the lower limbs, increasing scientific evidence supported its use in this limited group. However, patients with prevalent conditions remained excluded from this initial boom of DRG-S. A frequent finding in postsurgical back pain is the formation of epidural scars constricting the dural sac and the spinal nerves. It is questionable whether epidural fibrosis is causative for failed back surgery syndrome (FBSS) (Geudeke et al., 2021; Masopust et al., 2021), but it definitely poses challenges to the percutaneous placement of thin epidural leads in neuroforamina. This is particularly difficult in the case of fibrosis causing foraminal stenosis.

Modern DRG-S was initially described and performed only for lumbosacral and lower thoracic levels. Puncture at lower levels is safer because the spinal canal is larger below L1/2 and the spinal cord is absent. Neuroforamina are also larger, opposing to foramina at cervical levels. Cervical DRG leads are placed close to the vertebral artery, which compresses ventral roots and the DRGs mostly between C3 and C6 (Alleyne et al., 1998). Another complicating factor is the thin layer of cerebrospinal fluid, increasing the risk of cervical punctures. Targeting cervical levels for DRG-S is certainly more complex, but certain causes of neuropathic pain occur solely or mostly in cervical or high-thoracic levels, such as intercostal neuralgia, postherpetic neuralgia, ulnar and radial nerve compression syndromes. There was little evidence about the safety and efficacy of cervical and high-thoracic DRG-S. It interestingly started with the report of Lynch et al, who stimulated the C2 DRG for postherpetic neuralgia with an SCS before DRG-S systems were available (Lynch et al., 2011). The case described by Garg and Danesh of accidental stimulation of the C6 DRG with an SCS lead due to epidural fibrosis in a patient with CRPS in the right arm is a debatable issue (Garg and Danesh, 2015).

DRG-S was initially used as the first isolated surgical treatment for suitable cases, but complex cases of neuropathic pain with prior neuromodulative procedures may still profit from the adding effect of modulation of the DRG. In a case report of Yang and Hunter, two patients CRPS were insufficiently treated with SCS despite exhaustive reprogramming und reported sustained pain improvement with additional DRG-S (Yang and Hunter, 2017). Depending on the cause of failure to SCS, which may be inadequate coverage of the painful area or the existence of a second important pain component, DRG-S might pose an adequate solution for different reasons. The combination of SCS and DRG-S as salvage treatment was poorly described in the literature but has relevance for a small group of patients that remain refractory even to advanced neuromodulation.

Choosing the target level is essential when performing DRG-S. Anatomical correlation with known dermatomes is important, but definitive confirmation of the chosen target can only be obtained through intraoperative testing, which is only possible in awake patients. The ACCURATE trial was done with local anesthesia

and many of the initial landmark studies as well (Deer et al., 2017, 2013; Liem et al., 2013). However, when treating patients with refractory chronic pain, psychological or cognitive issues may play an important role and surgical procedures may not be possible under these circumstances. There is a need for an additional, fast technique that could substitute the role of intraoperative testing and allow the implantation of DRG-S leads under general anesthesia with more safety than choosing the target on anatomical basis alone. Hunter et al. published a case report of successful selective radiofrequency stimulation to predict the targets for DRG-S in patients with postamputation pain, when no clear anatomical correlation can be obtained (Hunter et al., 2017). Despite the discussion, whether an electrical or chemical block would be most appropriate for this purpose, there is no validation of such a technique. The real benefit of such a preoperative test enhancing the safety of DRG-S performed under general anesthesia is still to be found.

Another issue of concern is the programming of stimulation parameters in DRG-S. There are clear anatomical reasons why DRG-S demands much less energy than SCS (Deer et al., 2017), and the fact that paresthesia-free stimulation is as effective as paresthesia-dependent programming (Mekhail et al., 2020a; Verrills et al., 2019) explain why stimulation amplitudes hardly achieve 1 mA. Little is known, however, about the effect of stimulation frequency over the outcomes of DRG-S. Similarly to SCS, high-frequency stimulation at 10 kHz was tested for the DRG in a total of seven patients with relative success (Billet et al., 2018, 2017). Koetsier et al. reported that low-frequency stimulation of 1 Hz showed a delayed wash-out effect in the treatment of painful diabetic neuropathy in rats. The first evidence in humans that sustained pain relief could be achieved with stimulation frequency of 4 Hz came from Chapman et al., who published a series of twenty patients without control group (Chapman et al., 2020b). There is currently no scientific evidence that demonstrated the benefits of certain frequency ranges. This is of importance for both maximum pain relief and prolongation of battery lifetime, as stimulation frequency is the most important determinant of output power.

1.4 Objectives

DRG-S is an elegant technique that addresses chronic neuropathic pain in a unique manner. The aim of this study is to optimize this procedure to make it more accessible for a larger contingent of patients with chronic pain and to maximize pain relief. In a first step, the focus will be technical issues regarding the implantation of DRG leads under complex conditions, discussing an open implantation procedure for selected cases and the technique and outcomes of cervical and high-thoracic DRG-S. After that, the synergetic effect of DRG-S with SCS will be considered for complex cases. Next, a proposal of preoperative test for confirmation of the target level for DRG-S performed under general anesthesia will be critically analyzed in a prospective study. Finally, the first randomized double-blind clinical trial comparing different frequencies in DRG-S will discuss important issues of stimulation programming and the mechanism of action of DRG-S.

2 Open Microsurgical Dorsal Root Ganglion Lead Placement

Piedade, G.S., Cornelius, J.F., Chatzikalfas, A., Vesper, J., Slotty, P.J.

Neuromodulation, 22: 956-959, 2019

Introduction

Dorsal root ganglion stimulation (DRG) is a new but well established neuromodulation technique allowing new indications and superiority to pre-existing stimulation techniques such as SCS in selected pain etiologies (Deer et al., 2016). With completion and publication of the ACCURATE study, DRG stimulation has become available in the US (Levy R, Deer T., 2015). Due to the system´s reduced stiffness and susceptibility to damage compared to traditional SCS systems, DRG implantation technique is more constrained to normal anatomical situations. Previous surgical procedures in the implantation area are considered contraindications for DRG stimulation surgery. Despite this, successful DRG implantation with good outcome has been performed in our center with percutaneous implantation technique in patients with previous surgery, such as total disc replacement and spinal decompression procedures.

In two of our patients we encountered anatomical changes due to previous surgeries, which despite multiple attempts and variations in approach rendered percutaneous lead implantation impossible. As we considered these patients ideal candidates for dorsal root ganglion stimulation regarding the anticipated therapeutic effect, we discussed the option of open lead placement. In both patients, an open microsurgical approach combining foraminotomy and visually controlled open lead placement resulted in a stable, radiographically correct and therapeutically effective lead position. This paper describes the basic approach and early outcome data. A video detailing the surgical technique is available online.

Methods

Open DRG lead placement was performed in two patients so far. Both patients had previous spinal procedures, which were directly linked to the development of chronic neuropathic pain. Patient No. 1 had a long history of mainly L5 radicular pain before undergoing spinal decompression surgery with foraminal decompression of L5 and S1 on the left. Following an uneventful intraoperative course, the patient reported severe L5 pain immediately after surgery. CT imaging revealed an epidural bleeding compressing the L5 root and immediate revision surgery was performed. This left the patient with a severe neuropathic L5 pain.

Conservative management did not result in sufficient pain reduction, periradicular infiltration of L5 reliably led to significant pain reduction for some weeks and 11 infiltrations were performed during the four years following surgery. A percutaneous DRG trial was performed in analgosedation aiming at the L5 and S1 roots on the left. Placement of the S1 lead posed no problem, but entry into the L5 foramen was not possible due to stenosis and the patient reported excruciating pain during the insertion (Figure 3). Therefore, surgery had to be stopped with only the S1 lead in place.

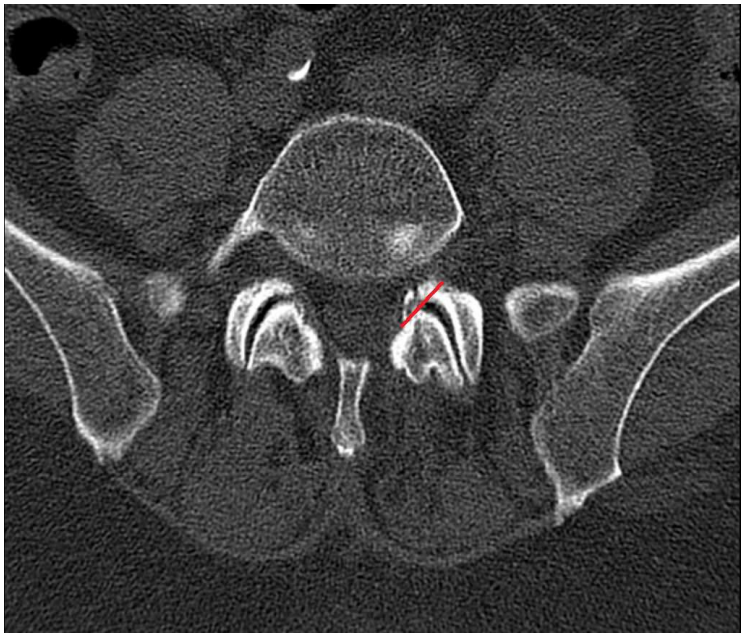

Fig. 3: Preoperative CT of patient no. 1 showing the foraminal stenosis making the percutaneous approach impossible, the degree of foraminotomy performed is given by

the right red line. Used with permission from John Wiley & Sons - Books (Guilherme S. Piedade et al., 2019).

Programming revealed that the area of pain could not be reached with the S1 electrode. We intensively discussed the situation with the patient and he consented to the attempt of an open lead placement. Surgery was performed in general anesthesia in a microsurgical manner. General anesthesia was chosen as the previous percutaneous procedure (esp. while trying to enter the foramen) was very painful for the patient and the extent of dissection and foraminotomy necessary for lead placement was not clear for the team. The S1 electrode had to be removed for the foraminotomy of L5. Following foraminal decompression and cranial epidural dissection for loop placement, both electrodes could be placed under visual and radiographic control (Figures 4 and 5). The lead delivering sheath was not used as it proved to be too flexible to provide sufficient push into the foramen, it was brought in place with bayonet forceps. Following radiographic and electrophysiological control with motor stimulation, epidural strain relief loops were made and stabilized with fibrin sealant patch and fibrin glue (Figure 6). No additional anchoring was performed. The electrodes were tunneled to the IPG pocket and connected to a Proclaim DRG. Wound closure was performed as in any spinal procedure.

Patient No. 2 is a 55-year-old female suffering from a severe complex regional pain syndrome (CRPS) in the left foot and lower leg following three spinal disc surgeries at L5/S1 and an S1 foraminal decompression. HF10 spinal cord stimulation did not result in significant pain relief. Similar to patient No. 1, percutaneous lead placement in S1 was successful and L5 was frustraneous due to foraminal stenosis. As S1 stimulation alone proved insufficient for pain control, an open approach was performed as described above, again resulting in a correct position of both leads.

Informed consent was obtained from the patients regarding analysis and publication of medical information and imaging.

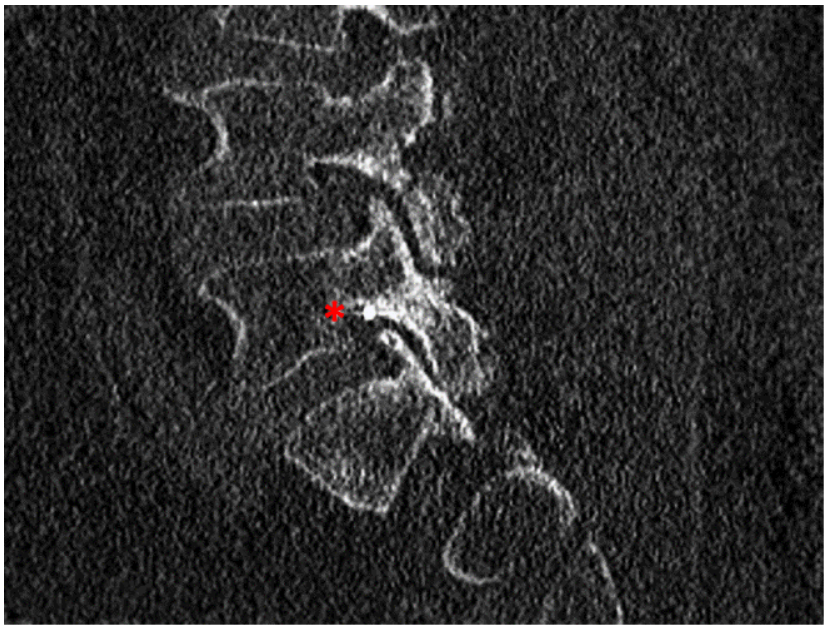

Fig. 4: Placed lead in sagittal view in patient no. 1. Used with permission from John Wiley & Sons - Books (Guilherme S. Piedade et al., 2019).

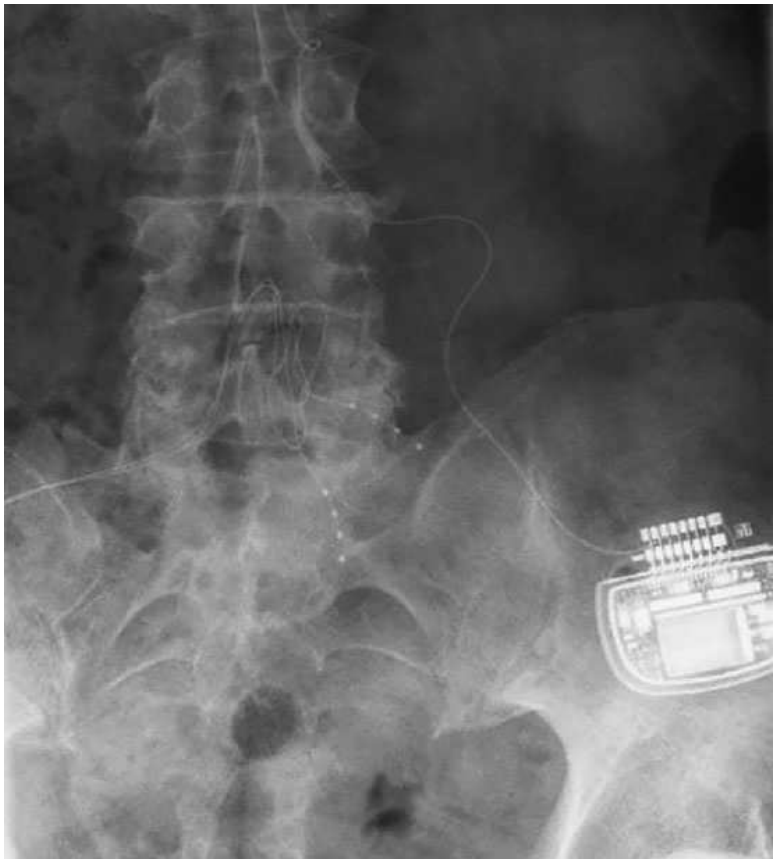

Fig. 5: Postsurgical X-ray in patient no. 1 showing the strain relief loops, the extend of cranial epidural dissection performed (approximately one level) can be seen from the extend of loops reaching cranially. Used with permission from John Wiley & Sons - Books (Guilherme S. Piedade et al., 2019).

Results

In both cases open DRG lead placement resulted in an electrophysiological and radiographic correct lead position. Surgery took about 90 minutes in both patients and was tolerated well with no adverse events. These were the only cases in which this technique was used. Early postsurgical programming resulted in excellent coverage of the pain area and good pain reduction. Changes in paresthesia coverage and stimulation intensity are commonly observed in the early phase of DRG stimulation. We experienced a higher rate of changes in stimulation intensity and coverage in our two patients with open lead placement compared to patients following percutaneous lead placement and reprogramming had to be done at a higher frequency during this early course of treatment. Stable programming parameters were achieved at three months following surgery.

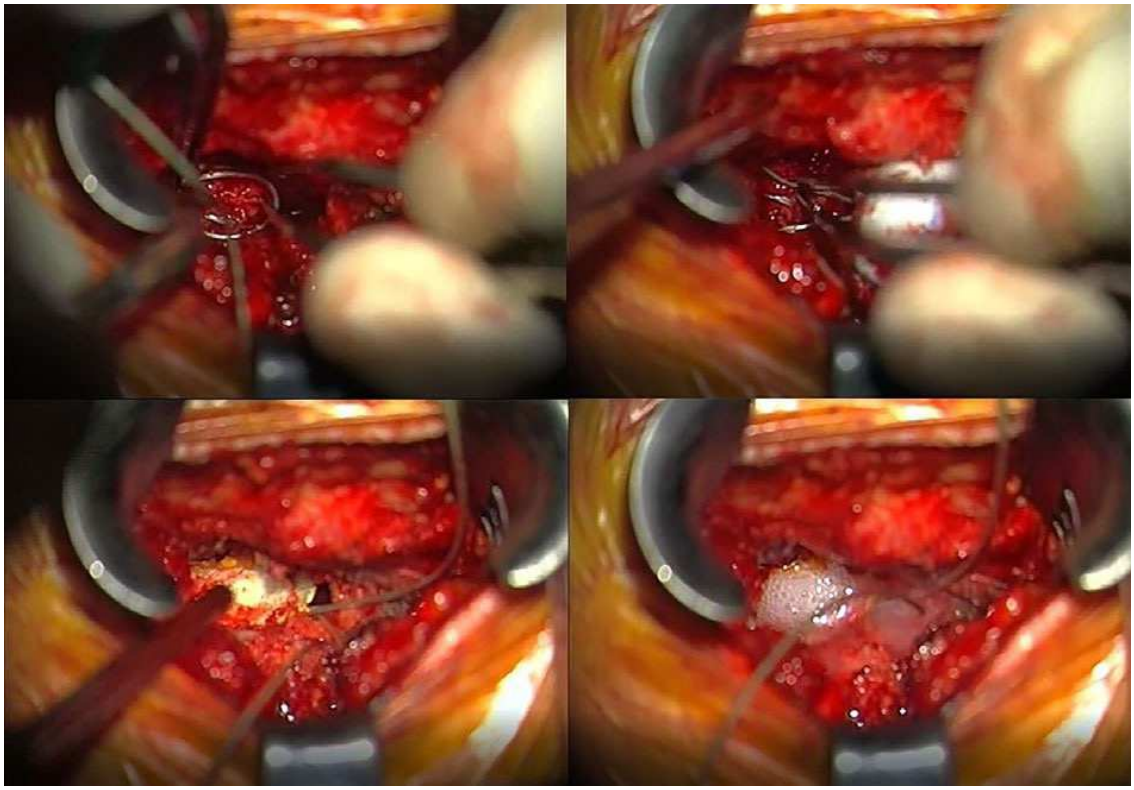

Fig. 6: Panel of microscope photos taken during surgery, from top left to bottom right showing bayonet forceps used to push the electrode into the foramen without the sheath, construction of strain relief loops, stabilization of the situation with fibrin patch and fibrin glue. For more details, please see the video available with the manuscript. Used with permission from John Wiley & Sons - Books (Guilherme S. Piedade et al., 2019).

Following a period of excellent pain control during the first months of treatment (from VAS 9 to VAS 2), patient no. 1 reported a new increase in pain which could not be controlled with DRG stimulation alone. This increase is mainly triggered by increased activity and he required periradicular infiltrations but at a much lower frequency than prior to surgery. Tentative deactivation of the system leads to a significant increase in pain and pain medication is still significantly reduced.

Unfortunately, patient no 2 did not receive reprogramming as required as she comes from a remote area. Reprogramming in our center was performed at 12 months follow-up and the patient reported good pain control for the first few weeks of treatment after which stimulation was not adjusted. She still reports a high variability of paresthesia coverage and stimulation intensity during movement. During reprogramming an excellent coverage of the pain area could be achieved.

Discussion

In numerous occasions the option of open DRG lead placement has been discussed at national and international neuromodulation meetings. Two key questions were commonly discussed in these situations. First of all was how to stabilize the lead and especially the strain relief loops in open placement. This question is crucial as commonly the lead and loops are stabilized in the epidural layer between dura and posterior bone of the laminae. In an open approach the lamina is reduced or completely removed and stabilization of the loops has to be achieved in other ways. In our case we choose a combination of fibrin sealant patch (Tachosil®) additionally stabilized by fibrin glue. The cranial portion of the loops was additionally placed in the cranial portion of the operating field in which the cranial lamina was intact.

The second question that commonly arose in discussions was whether a special tool is required for open lead placement or if the percutaneous tool (sheath) can be used. In our experience, the sheath does not provide the required stiffness to allow open lead placement. Forward push of the electrode resulted in

dorsal bending of the sheath. Following a couple of frustraneous maneuvers final lead placement was possible with a bayonet forceps. Dissection in the foramen had already been done during foraminotomy using ball-end hooks. Handling the lead with two forceps allowed precise maneuvering of the electrode to dorsally place of the electrode and create the strain relief loops.

Based on our first experience we do not see the necessity to design a special tool for open DRG placement for two reasons: cases with previous surgery in the spinal area or even in the foramen itself that impede percutaneous lead placement are rare, and analyzing the cases in which open DRG placement is necessary, anatomical variations created by previous surgery are too variable to design a one-fits-all tool. For surgeons with sufficient experience in spinal surgery, required tools are already found in the neurosurgeons' armamentarium. Both patients clearly suffered from neuropathic pain and foraminal decompression (which had to be performed for lead placement in both patients) alone was not sufficient for pain control. At 18 months follow-up patient No. 1 clearly required DRG stimulation to sufficiently suppress his pain. In patient No. 2 the therapeutic efficacy could not be finally assessed due to the lack of reprogramming, paresthesia coverage indicates however an excellent and unchanged lead location at 12 months.

This paper focuses on the surgical technique used for open DRG lead placement. The existence of differences in programming, long term outcome or overall efficacy of DRG stimulation following an open approach should be determined in a larger group of patients. The technique described proved feasible for lead implantation without special tools and the technique of loop stabilization resulted in no dislocation at 12 and 18 months. However, as only two patients have been treated so far, conclusions should be drawn very carefully.

Conclusion

Open DRG lead placement is possible, stable and effective using a combination of the provided lead system and common spinal surgical techniques. A combination of fibrin sealant patch, cranial epidural dissection and loop placement and fibrin glue can provide sufficient loop stability and thereby

compensate for previous decompressive spinal surgery. Open DRG placement might be considered in promising cases in which the percutaneous implantation technique fails due to epidural scaring and foraminal stenosis.

3 Cervical and High-Thoracic Dorsal Root Ganglion Stimulation in Chronic Neuropathic Pain

Piedade, G.S., Vesper, J., Chatzikalfas, A., Slotty, P.J.

Neuromodulation, 22: 951-955, 2019

Introduction

The dorsal root ganglion (DRG) is one of the key structures in the development of neuropathic pain. It is a subdural structure, which contains the cell bodies of the primary sensory neurons. In neuropathic pain, lower potential threshold and subsequent spontaneous firing can be observed in the DRG cells (Koopmeiners et al., 2013). Low frequency stimulation can lower this abnormal activity by readjusting the potential threshold (McIntyre et al., 2004). In pathologies involving autonomic changes such as complex regional pain syndrome (CRPS), this readjustment even partially reverts autonomic changes by means not completely understood (Croom et al., 1997). DRG stimulation offers several advances over traditional spinal cord stimulation on selected etiologies: each DRG covers a selected dermatome and therefore allows more precisely targeted stimulation compared to SCS with a stronger potential of pain suppression (Liem et al., 2013).

DRG stimulation received its CE mark in the European Union in 2011, later in 2015 the ACCURATE study proved the superiority of DRG stimulation in CRPS patients compared to conventional tonic SCS at 3 and 12 months follow-up (Liem et al., 2015, 2013). This landmark study led to FDA approval of DRG stimulation in the U.S. in February 2016. Indications are limited to chronic neuropathic pain associated with CRPS or peripheral causalgia, anatomical area for implantation is limited to sacral, lumbar and the lower (T10 and below) thoracic nerve roots as well. In Europe, supranational approval does not include any anatomical limitations and the system is approved for treatment of chronic neuropathic pain regardless of origin.

Many pathologies treated with DRG stimulation such as CRPS and chronic pain following peripheral nerve damage are not limited to the lower extremity. These diseases can also be found in the upper limbs and are therefore possibly promising targets for DRG stimulation. Additionally, certain conditions like intercostal neuralgia and post-herpetic neuralgia primarily exist in the thoracic region and therefore pose possible targets.

The particularities of DRG stimulation in the cervical and thoracic spine go beyond the surgical technique and involve programming, motor-stimulation thresholds and variability of long-term stimulation efficacy. Although many studies were published on DRG stimulation for chronic pain in the lower extremities, little is known about the short and long-term effects of this therapy for thoracic and upper limb pain. We report on a consecutive series of twenty cases of cervical and high-thoracic DRG stimulation.

Material and methods

We report on a consecutive series of 20 patients treated with DRG stimulation (in 19 cases Axium™ System, Spinal Modulation, CA, USA; in one case Proclaim™ DRG Neurostimulation System, Abbott (formerly St. Jude Medical), IL, USA). All patients underwent dorsal root ganglion stimulation in the upper thoracic or cervical spine at the Department of Functional Neurosurgery and Stereotaxy of the Heinrich-Heine-University Düsseldorf between February 2013 and October 2016. All patients were aged 18 years or older and suffered from refractory chronic pain due to peripheral nerve or brachial plexus injuries, spinal cord surgery, post-herpetic neuralgia, CRPS II or phantom limb pain. All patients were subject to multidisciplinary pain treatment prior to referral to our department. Electrode implantation was performed in general anaesthesia in all patients, in most cases following a nerve root block to define the affected level. This was generally done in an outpatient setting under CT guidance. Electrode implantation technique differs from lumbar implantation: the needle position general has to be steeper in both the lateral and cranio-caudal direction and especially in the cervical spine a same level approach is usually necessary. Maneuverability of the implantation system is generally very limited due to the

thin CSF layer and the spinal cord. All patients were trialed with externalized electrodes (with extensions) for 3-7 days; a successful trial was defined as at least 50% pain relief. Pain reduction was evaluated using the VAS scale. Patient data was prospectively collected and patient consent for data collection and publication was obtained prior to trialing. Follow-up data was collected during out-patient visits which were part of the clinical routine. This study was approved by the local REB (internal no. 4077).

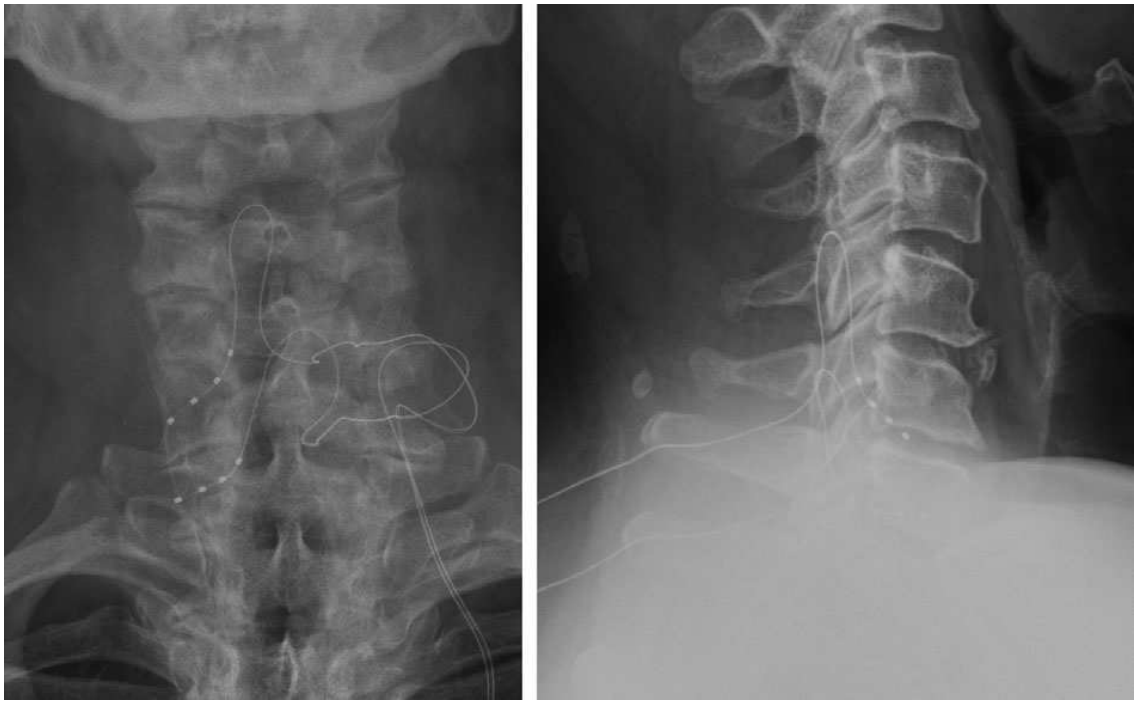

Fig. 7: Early postsurgical lateral and a.p. x-ray of patient no. 10 with two DRG-electrodes in the C7 and C8 neuroforamen on the right side. Note the limited value of lateral x-ray in this region because of the shoulder girdle. Used with permission from John Wiley & Sons - Books (Guilherme Santos Piedade et al., 2019).

Results

Overall, 20 patients were assessed for cervical or high-thoracic DRG stimulation after having failed multidisciplinary best medical treatment for their condition. Mean age at time of implantation was 50.6 (SD 9.68) years (Table 1). Indications varied among CRPS (5 cases), peripheral / plexus nerve injury (7 cases), post-herpetic neuralgia (2 cases), post-spine surgery pain (5 case) and phantom limb pain (1 case). Of these patients, 90.0% (18/20) received a

permanent neurostimulation system after having a successful trial period. In all patients, the IPG was implanted in the lower back, in most cases extensions were used in final implantation due to long route from electrode insertion point to the IPG. Patients with positive trial results had a mean overall perceived pain of 8.5 (SD 1.04) prior to implantation.

Six patients had one electrode implanted, nine received two electrodes and two patients a total of three (Figures 7 and 8). The overall pain perception at 3 months follow-up was 3.2 (SD 2.33) (n = 18), which calculates as an average pain relief after 3 months of 60.9%. Overall 77.8% of the patients had a positive short-term response. No early positive response was seen in three cases of peripheral nerve injury and in one post-herpetic neuralgia case. Early reduction in treatment effect requiring reprogramming was commonly observed during the first few months of treatment, a permanent loss of effect in the long-term refractory to reprogramming was found in one case of post-herpetic neuralgia and in one patient with post-surgical pain. The overall pain at 6 months follow-up was 3.9 (SD 2.25) (n = 13) and at 12 months 3.8 (SD 1.64) (n = 9).

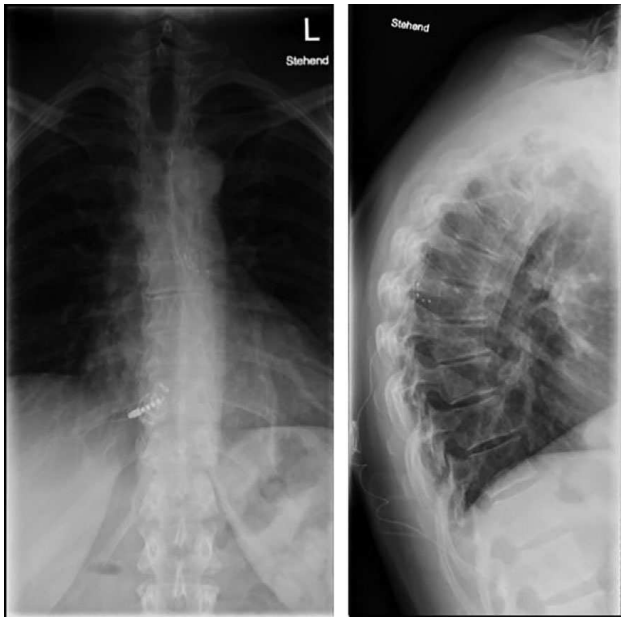

Fig. 8: Thoracic lead placement in T7 in a rare case of DRG stimulation used for neuropathic pain on the left arm after the resection of a medullary hemangioblastoma. Lateral view confirms correct lead position. The patient achieved significant short- and long-term pain relief. Used with permission from John Wiley & Sons - Books (Guilherme Santos Piedade et al., 2019).

Table 1. Pain development following successful trials and permanent implants.

No.	Age	Pain etiology	Underlying pathology	Lead location	VAS baseline	VAS @ 3 f/u	VAS @ 6 f/u	VAS @ 12 f/u
1	51	Resection of hemangioblastoma	Post-surgical pain	T7 left	8	2 (-75%)	4 (-50%)	3 (-62.5%)
2	68	Use of interferon for melanoma	Nerve injury	C8 left + right	10	2 (-80%)	2 (-80%)	2 (-80%)
3	55	Clavicle fracture	Nerve injury	C4 + C5 left	8	3 (-62.5%)	4 (-50%)	4 (-50%)
4	41	Arthroscopy	CRPS	C6 + C7 right	8	3 (-62.5%)	4 (-50%)	4 (-50%)
5	48	N. ulnaris decompression	CRPS	C8 left	9	1 (-88.9%)	2 (-77.8%)	2 (-77.8%)
6	52	Trauma	Nerve injury	C6 right	8	6 (-25%)	6 (-25%)	5 (-37.5%)
7	44	Disc herniation	Post-surgical pain	T1 + T2 right	9	3 (-66.7%)	4 (-55.6%)	6 (-33.3%)
8	61	Herpes zoster	Post-herpetic neuralgia	C8, T1, T2 right	8	3 (-62.5%)	6 (-37.5%)	6 (-37.5%)
9	51	Resection of arachnoid cyst	Post-surgical pain	T5 + T9 left	9	1 (-88.9%)	1 (-88.9%)	2 (-77.8%)
10	46	Radiotherapy for breast cancer	CRPS	C7 + C8 right	10	0 (-100%)	0 (-100%)	n/a
11	40	Clavicle fracture	Nerve injury	C4 + C5 right	7	6 (-14.3%)	6 (-14.3%)	n/a
12	41	Resection of neuroma	CRPS	C6 + C7 right	10	3 (-70%)	4 (-60%)	n/a
13	53	Carpal tunel release	Nerve injury	C7 right	8	8 (0%)	8 (0%)	explantation
14	51	Abscess drainage in axilla	CRPS	T1 + T2 right	7	2 (-71.4%)	n/a	n/a
15	45	Disc herniation	Post-surgical pain	C6 left	8	0 (-100%)	n/a	n/a
16	38	Arm amputation	Phantom pain	C7 + T1 left	10	5 (-50%)	n/a	n/a
17	51	Spinal stenosis	Post-surgical pain	C8 left + right	9	2 (-77.8%)	n/a	n/a
18	75	Herpes zoster	Post-herpetic neuralgia	T4, T5, T7 left	7	7 (0%)	explantation	n/a

Table 1: Pain changes given in % compared to baseline. Used with permission from John Wiley & Sons - Books (Piedade et al. 2019).

In one patient, a transient paresis of the arm and hand was observed immediately following electrode implantation after an uneventful surgery. Immediate CT showed a regular electrode position with no epidural bleeding or significant stenosis caused by the implants, no signs of spinal cord injury were seen being aware that CT is limited in showing such alterations. The electrodes were left in place and the patient was trialed successful. Permanent implantation was performed and the paresis completely resolved within three months. Two patients had their systems removed due to inefficacy. In three cases, revision-surgery of the leads and extensions was necessary due to dislocation or rupture. The small diameter and low mechanical resilience of the leads and extensions seem to pose a problem considering the long route down the IPG pocket, comparable to mechanical complications seen in ONS surgery.

Discussion

Similarly to the ACCURATE study, which evaluated DRG stimulation only for groin and lower limb pain and found 81.2% responsiveness at 3 months follow-up (3), 77.8% of the patients of our case series achieved a satisfactory short-term result. Our long-term success rates are unfortunately not representative due to a loss of follow-up. Huygen FJPM et al. published in 2015 a comparable case series of 19 patients with upper limb neuropathic pain treated with DRG stimulation, most of them with CRPS. A lower trial-to-permanent success rate was found (84.2%), the average pain relief at 3 months follow-up of 57.3% was similar to our results (Frank J. P. M. Huygen, G. Baranidharan, K. Simpson, N. K. Patel, S. Love-Jones, A. L. Green, J. J. Fitzgerald, 2014).

Although very similar, cervical and high-thoracic DRG stimulation has important particularities that make success and complication rates differ when compared to traditional stimulation for groin and lower limbs. Some pain etiologies are specific of the chest wall and upper limbs, such as intercostal neuralgia and post-herpetic neuralgia. Treating post-herpetic neuralgia (PHN) is a major problem, it has challenged pain physicians and neurosurgeons for decades. The results we are observing with DRG stimulation so far are somewhat mixed (Kim et al., 2017; Lynch et al., 2011; Yanamoto and Murakawa, 2012). No

comprehensive overview has been published so far and no common sense inside the neuromodulation society exists regarding recommendation for DRG stimulation in PHN. In our experience, stimulation of the affected ganglion itself does result in immediate and unbearable increase in pain under stimulation. Using the overlapping of dermatomes stimulation of adjacent segments does lead to a decrease in pain levels, especially regarding allodynia. This effect anyhow was only short termed in our experience and could not be regained by intensive programming or stimulation holiday. We therefore would currently not generally recommend DRG stimulation in PHN, well aware that other experts in this field would disagree.

Some procedures restrict to upper limbs and thorax are classic causes of neuropathic pain that can be treated with neurostimulation. Nerve compression syndromes in the upper extremity such as ulnar and radial nerve compression are common and decompression surgery leaves a considerable number of patients with chronic pain syndromes and neuropathic pain(MacDonald et al., 1978). Cervical and upper thoracic DRG stimulation offers a valuable option in these patients and excellent results are seen in these patients.

Our case series includes one etiology in which DRG stimulation has to the best of our knowledge not been described for: neuropathic pain following resection of spinal tumor at T2-3, in this case a medullary hemangioblastoma. The patient had radiating pain to the left arm, which led to the diagnosis of a medullary tumor. Following resection of the tumor in another hospital, the pain did not subside and became chronic. She presented with constant scapular pain and exertional radiation to the left arm and to the ventral chest wall. A significant short- and long-term pain relief was achieved after the placement of a lead in T7 left. Going into an anatomical region with DRG electrodes in which complex medullary surgery had been performed crosses the border of what we currently think our stimulation hardware is suitable for and which indications can be covered by DRG stimulation.

DRG stimulation of cervical and high-thoracic spinal ganglia deserves special technical considerations. Due to anatomic differences, needle placement should take a steeper approach through the interlaminar space to reach the target

neuroforamen. The presence of the spinal cord (as opposed to the cauda equine in the lumbar region), the thin CSF layer and the unavoidable steeper approach lead to an increased risk of spinal cord lesion. A too lateral needle entry point intending to reduce dorsal pressure on the spinal cord will likely increase the risk of a ventral electrode position, leading to motor stimulation. Lead dislocations are likely more frequent in cervical DRG stimulation due to the high and frequent mobility of the spine in this region. In almost all cases, extensions were used due to trialing with permanent electrodes and due the long route from electrode to IPG pocket. As in occipital nerve stimulation, subcutaneous strain-relief loops turned out to be useful, but extensions fracture requiring revisions surgery were observed. In these cases, the insulation of the extension was intact, whereas the wire inside was torn. This was visible on x-ray in all cases. With this complication observed, surgery for the extensions and IPG might have to be reevaluated. A pectoral IPG pocket might offer a good alternative.

Conclusions

Cervical and upper thoracic DRG stimulation is feasible and results in good overall response rates to trialing and excellent long-term pain relief in primary responders. A modified surgical approach has to be used when compared with lumbar DRG electrode placement. Surgery itself in this region is more complication prone and challenging. Implanters should be in depth familiar with lumbar DRG implantation technique and spinal surgery in the thoracic and cervical region.

4 Synergetic efficacy of simultaneous DRG- and traditional spinal cord stimulation

Piedade, G.S., Vesper, J., Slotty, P.J.

Acta Neurochir (Wien), 162: 257-260, 2020

Introduction

Dorsal root ganglion (DRG) stimulation achieved general acknowledgment after the results of the ACCURATE study, which showed superiority of the new therapy when compared to the conventional tonic spinal cord stimulation (SCS) in the treatment of complex regional pain syndrome (CRPS) of the lower limbs (Deer et al., 2019a). DRG stimulation, now approved by the FDA, was established as an independent treatment modality that has since then been preferred for focal chronic pain, with normally distinctive nerve roots affected. The fact that DRG stimulation allows more precise targeting of stimulation and likely a higher degree of pain relief made it also a valuable resource for certain patients already under spinal cord stimulation that achieved insufficient results.

Most of the failures of spinal cord stimulation occur in spite of sufficient paresthesia on the target area, as reported by Jang et al., and this is particularly more frequent in the case of postherpetic neuralgia, spinal cord lesions and in patients with allodynia dominant pain (Jang et al., 2008). In the remaining 34% of the reported failures, reprogramming and lead revision are effective to solve loss of treatment efficacy, but some complex patients remain with insufficient stimulation results. Not only anatomic variations or the variability of SCS lead positions may play a role, but patients may first become aware of a different, more focal pain component when the general back pain is partially treated or the other way around. For the cases of complex chronic pain that overcome the therapeutic possibilities of spinal cord stimulation alone, DRG stimulation may complement results and even provide a more efficient stimulation pattern. Little is known about the feasibility and the efficacy of this combined approach.

Methods

We report a series of 5 patients treated with dorsal root ganglion stimulation and spinal cord stimulation at the Department of Functional Neurosurgery and Stereotaxy. The first procedure was performed in February 2011, the last one in June 2018. In the five cases, pain was restricted to the back and lower limbs and was refractory to multidisciplinary pain treatment. Prior to SCS system implantation, all patients were trialed and reported at least 50% pain relief. Before implantation of a DRG stimulation system, a CT-guided selective nerve root block confirmed the affected level (Wagner, 2004). Pain reduction was evaluated using the VAS scale, the first baseline consisting of pain level in the four weeks preceding the first procedure. The second baseline considered both the pain treated with the first procedure and the new or insufficiently treated preexisting pain component. The pain reported 12 months following the second procedure combining the efficacy of both stimulation methods was also assessed. Data of patients with simultaneous SCS und DRG stimulation were selected from a larger prospective study (IRB approval no. 4077).

Results

A total of five patients with simultaneous SCS and DRG stimulation were included. In the same period, for a matter of comparison, there were 117 implantations of a DRG stimulation system and 913 of an SCS system at the same Department. Four patients had a primary spinal disease that needed a surgical treatment and developed a failed back surgery syndrome (FBSS), etiologies included spinal fracture, disc herniation and spinal stenosis. In one case a chronic regional pain syndrome type II emerged after an ankle fracture. The average age when the first procedure was performed was 54.8 years, most of the patients were male (4/5). SCS was the first procedure of choice in four cases and without exception led to a significant pain relief. Patient 3 was the only one to be primarily treated with DRG stimulation because of his pain character mainly localized in the groin, which could also be adequately treated with a single electrode in L2. The time until a second procedure varied between 4 and 90 months and was in average 32.2 months (Table 2).

Table 2. Pain development following both neurostimulation procedures.

Patient	Age	Etiology	Pathology	1st Procedure	Interval (mo)	2nd Procedure	VAS Baseline 1	VAS Baseline 2	VAS @ 12 f/u
1	62	Spinal fracture	FBSS	SCS Th9-10	4	DRG L1-2	9	3 (-67%), 7	3 (-57%)
2	52	Disc herniation	FBSS	SCS Th6-7	90	DRG S1	9	4 (-56%), 8	3 (-63%)
3	64	Spinal stenosis	FBSS	DRG L2	5	SCS Th10-12	9	2 (-78%), 8	2 (-75%)
4	43	Ankle fracture	CRPS	SCS Th7-11	11	DRG L4-S1	10	5 (-50%), 8	7 (-13%)
5	53	Spinal stenosis	FBSS	SCS Th8-10	51	DRG S1	8	3 (-63%), 10	5 (-50%)

Table 2: The age at the time of the first procedure was presented. Interval between the procedures was indicated in months and pain intensity in the VAS scale. The first baseline indicates pain intensity in the four weeks preceding the first procedure, the second baseline considers both the pain treated with the first procedure (with percentage change) and the new or insufficiently treated pain component prior to the second procedure. Pain intensity of this second painful component is reported in a 12-month follow-up. Used with permission from Springer Nature (Piedade, Vesper, and Slotty 2020).

In the first two cases and in patient 5 the SCS was even after extensive reprogramming not technically able to reach distant pain areas, leaving a significant focal pain area untreated. Patients 3 and 4, however, reported another much more relevant pain after the first procedure in areas not covered by stimulation. Patient 3 was unsatisfied with a back pain that he first noticed after adequate treatment of his groin pain with DRG stimulation (Figures 9 and 10), patient 4 perceived a significant increase in his known sciatica after alleviation in his CRPS with SCS as the first procedure.

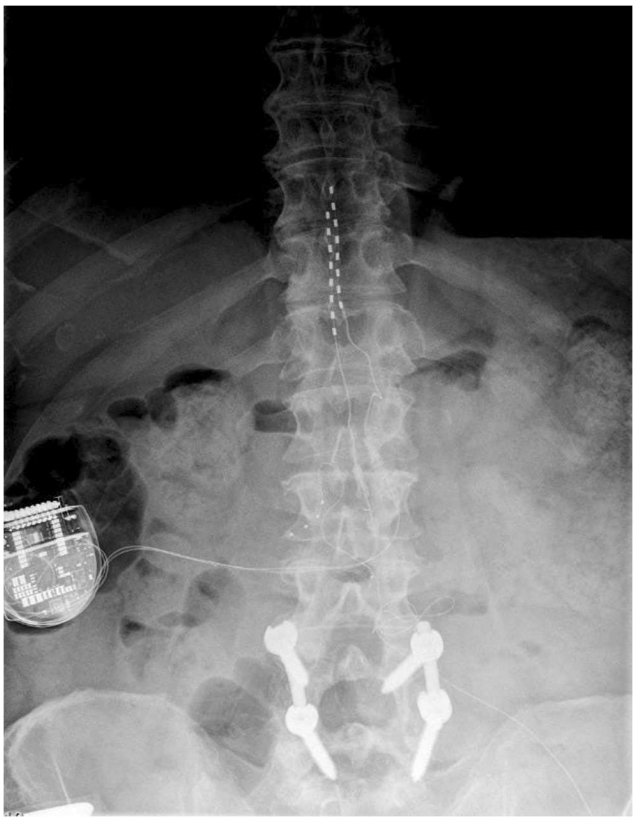

Fig. 9: X-ray of patient 3 suffering from groin pain on the right following a herniotomy and a severe FBSS with mainly leg pain. Used with permission from Springer Nature (Piedade et al., 2020).

All patients except number 4 had a significant pain relief after the second procedure. Patients 1, 2 and 5 had an adequate coverage of the residual pain after SCS, the localized residual painful area could be appropriately targeted with DRG stimulation following a previous test with nerve root block. The newly perceived lumbago of patient 3 could be addressed with an SCS, used only this

time as a second procedure. The patient 4, with a CRPS, reported continuous relief of his original pain with an SCS, but DRG stimulation from L4 to S1 afterwards was not capable of significantly changing the old sciatica despite adequate coverage.

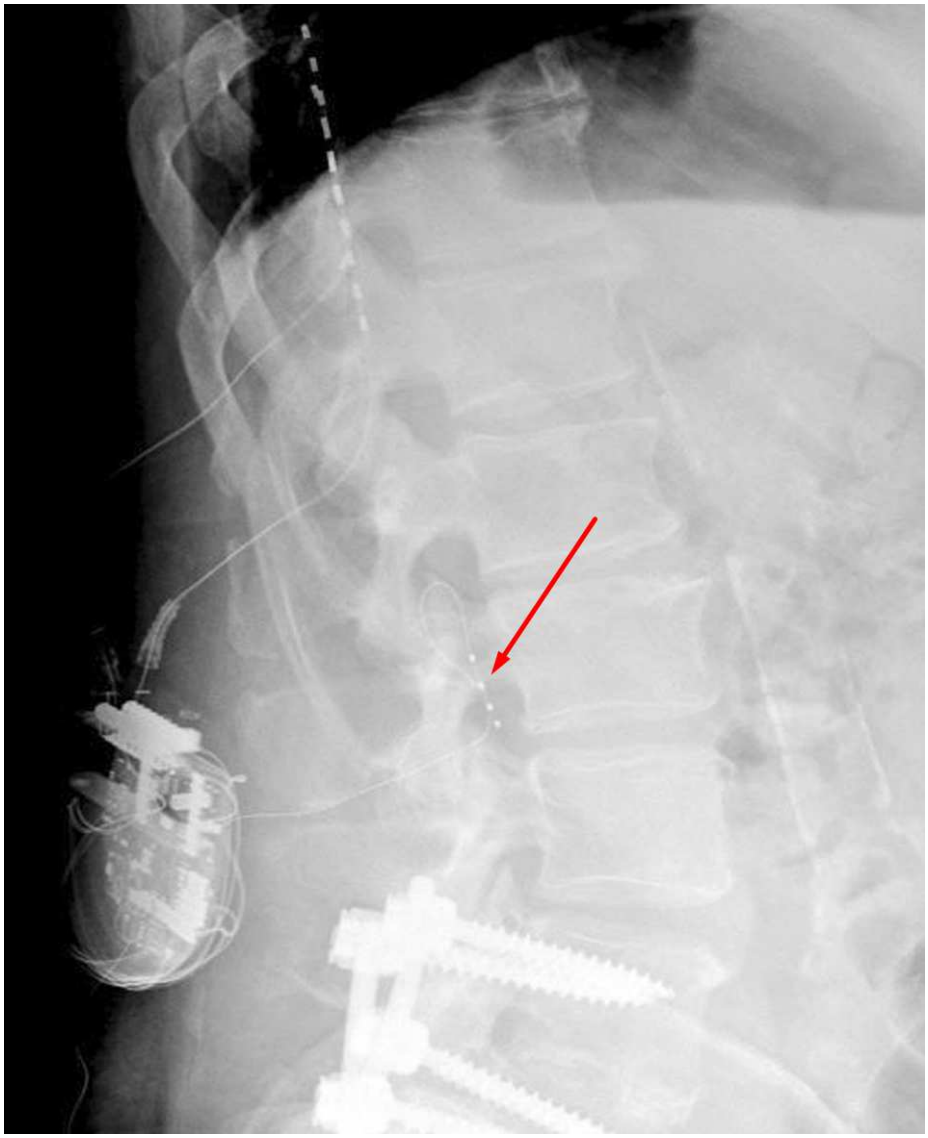

Fig. 10: Lateral x-ray of the same patient 3, note the DRG lead running cranial and dorsal in the foramen. Used with permission from Springer Nature (Piedade et al., 2020).

Programming had to be performed for each device individually with the other device switched off, allowing the patients to distinguish between paresthesia induced by each stimulation method. No technical difficulties or interferences were observed during programming or with the systems running. In all patients both systems were activated. For the surgical planning detailed

analysis of the already implanted components was performed mainly based on x-ray and, in some cases on cat scans. No surgical complications were encountered. Except in patient 2, that had a Specify® SCS system produced by Medtronic, all others neurostimulation systems implanted in this study were offered by Abbott - Progidy® in three cases and Eon Mini in one case for SCS®, Proclaim® in three patients and Axium® in the remaining two for DRG stimulation. In all patients, both IPGs were implanted dorsally.

Discussion

The need of a second functional procedure could be explained by a failure of the first procedure to completely cover the preoperative pain, which is a very superficial and intuitive answer that, however, hardly relates to the complexity of most patients submitted to multiple neuromodulation techniques. Cases 1, 2 and 4 indeed illustrate how DRG stimulation can appropriately address the more focal pain left untreated by an SCS with a huge stimulation area even after extensive reprogramming. Even with all currently available complex stimulation paradigms as burst, high density, high frequency, microdosing and so on, traditional SCS is limited by the rather large area of effect, which might result in overstimulation in some areas and insufficient (under-) stimulation in others (Deer et al., 2019a). Some patients, normally the most complex and chronically compromised ones, are affected by various, different pain components and their perception of them can be changed when the most intense pain component is treated. Patient 3 did not even perceive his back pain before his groin pain was successfully addressed by DRG stimulation.

Dorsal root ganglion stimulation and spinal cord stimulation used together have interesting clinical results and pose little additional technical and surgical challenges. As the spinal segments responsible for the lower limbs are significantly higher than their correspondent lumbar dorsal root ganglia, the risk of lead dislocation during a second procedure is low. This might differ significantly in other areas of the spine. Especially in the cervical spine, anatomical targets to treat FBSS of the neck and upper extremity pain are very close to each other and combining SCS and DRG in this area is likely surgically more challenging. We do

not have experience with a combination therapy in this area yet, despite our large series of cervical and high-thoracic DRG stimulation (Guilherme Santos Piedade et al., 2019). As in any other operative system revision, the risk of damage to the already implanted system in a second operation is always present but was not observed in the patients reported.

DRG stimulation and SCS complement each other for the case of remaining pain area, and to achieve optimal results the dedicated neuromodulist should be deeply familiar with both stimulation methods. Although insufficient pain relief remains as the major problem, unrequired paresthesia is also an issue of concern for patients with a stimulation area that is much larger than necessary to treat a more limited pain. SCS has comprehensively a high proportion of unrequired paresthesia, reaching 210% of the patients' total painful body surface area in a study conducted by Deer et al. Even burst and similar designs provoke paresthesia with high amplitude. The combination with DRG stimulation, that reaches an unrequired paresthesia of only 20% of the painful area in the same study (Deer et al., 2019a), could bring more comfort to patients. In this setting, integration of stimulation devices could avoid the shortcomings of two simultaneous and separate stimulation systems.

Implantable pulse generators (IPG) currently available in the market were developed either for SCS or for DRG stimulation. Patients benefiting from both treatments have the inconvenience of carrying two IPGs, that normally need to be replaced separately too. The development of hybrid IPGs, for both SCS and DRG stimulation, is feasible with the current technology and could reduce the total number of surgical procedures in the lifetime of an integrated stimulation system. There are already commercially available IPGs that use a similar principle and layer different waveforms simultaneously and therefore enable a combination therapy (Morales et al., 2019), but the system is currently restricted to SCS. An IPG compatible with both therapies should be able to deliver waves with high amplitude for SCS, enough to stimulate the spinal cord across the dura mater, and low amplitude for DRG stimulation, because in this last case the electrodes are surrounded by cerebrospinal fluid.

Conclusion

The combination of dorsal root ganglion and traditional spinal cord stimulation is surgically and technically feasible. In selected patients, the combination of both methods offers an option to alleviate pain states not sufficiently or not efficiently treated with one method alone. This introduction of IPGs combining SCS and DRG stimulation paradigms might increase acceptance of this option.

5 The role of periradicular infiltration in dorsal root ganglion stimulation for chronic neuropathic pain

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Introduction

The therapy of chronic neuropathic pain remains a challenge today. To date, only 30% to 40% of patients with neuropathic pain can be treated satisfactorily with medication alone (Arbeitsgruppe zur Erstellung der S3-Leitlinie et al., 2011). Conventional spinal cord stimulation (SCS) has been used successfully since 1967 to treat neuropathic pain. Yet, the results are not completely satisfying in all patient populations. The dorsal root ganglion (DRG) offers a relatively new target for neuromodulation due to its important role in the development and maintenance of chronic pain, as well as its anatomically convenient accessibility. DRG stimulation represents an effective supplement to SCS by providing precise, targeted stimulation even of discrete pain regions in areas that are difficult to reach with conventional SCS and improved patient outcomes for certain pain disorders (Krames, 2015). The ACCURATE study has shown that DRG stimulation provides long-term, sustained pain relief for specific pain disorders and painful regions, being superior to conventional tonic SCS in 3 and 12-month studies (Deer et al., 2017). Targeting the correct spinal level is essential for a successful pain treatment. Moreover, the number of electrodes is limited to 4 by the contacts of the implantable pulse generator and, each additional electrode increases the risk of surgical complications, such as infection or dislocation.

The initial selection of the correct DRG for stimulation is mostly based on the pain distribution among dermatomes. After a spinal level is targeted, a DRG stimulation lead is normally implanted with an extension lead externalized for a stimulation trial. If the patient benefits from this trial, the implantable pulse

generator (IPG) can be inserted in a second procedure. Alternatively, both leads and IPG can be implanted in the same procedure, all-in-one. The issue is that an anatomical selection of the DRG alone is not ideal since the pain area is not necessarily confined to the borders of the dermatomes. Additionally, dermatomes often show unique distributions with overlap.

In the literature, selective radiofrequency (RF) stimulation of the DRG has been discussed as a method for predicting the correct spinal level for stimulation, possibly giving important information for lead implantation in a stimulation trial or even in an all-in-on procedure (Hunter et al., 2017). Only two case studies on RF stimulation prior to DRG stimulation have been published so far; no standard preoperative procedure for DRG stimulation has been established yet. As a result, most surgeons have their own approach to solve the problem of pre-surgical targeting. A frequently used alternative is a CT-guided periradicular infiltration therapy (PRT). This procedure uses local anesthetics and can be easily performed on the preoperative day, efficiently helping the surgeon to choose the spinal level for DRG stimulation. There are no valid data associating PRT results with DRG outcomes so far. This study aims to establish the role of PRT in a preoperative assessment of the correct level for DRG stimulation regarding the coverage of the painful area with stimulation-induced paresthesia.

Methods

This is a prospective single-arm study that evaluates the outcomes of patients undergoing implantation of a DRG stimulation system. Twenty patients scheduled for DRG stimulation were prospectively observed between 2016 and 2018. All patients were at least 18 years old with an indication for DRG stimulation due to a chronic pain disorder refractory to best pharmacological treatment. No patients were excluded due to previously known intolerances to local anaesthetics administered as part of PRT or to other contraindications to the procedure.

The baseline pain assessment was performed using visual analogue scale (VAS). On the same day or in the following days a PRT of the presumptive affected DRG was performed (Wagner, 2004), the target level was chosen on a

clinical basis and in some cases multiple levels were chosen because the clinical examination by the responsible surgeon showed that the pain extended over several dermatomes. In our institution, a diagnostic PRT consists of the injection of bupivacaine 2,5 mg/mL. In cervical roots, 2 mL are the maximal injected volume, while in lumbar roots generally 3 mL are used. Dexamethasone is injected with bupivacaine only in therapeutic PRTs and was therefore not used. Bupivacaine has an elimination half-life of 143 minutes following epidural administration (Burm et al., 1987) and the PRT is performed at least 24 hours before lead implantation. Patients were clinically evaluated by the responsible surgeon up to 2 hours after the PRT, sensibility to light touch was assessed with either a tissue or cotton. During the consultation, the patient was asked about pain relief and to what extent the painful area was covered by the PRT (completely, partially, not at all). PRT testing was considered positive if patients responded with pain relief in the corresponding painful area. Complete pain relief was not required for a positive PRT assessment, as the goal was to find the appropriate level of stimulation and not to achieve complete pain relief with PRT. If the anesthetized region and the pain region were not congruent, another PRT of a different, usually adjacent spinal level was performed usually one day after the first one at the discretion of the responsible surgeon. After congruent PRT results to the painful area, lead placement was performed for trial stimulation or exceptionally in an all-in-one procedure. At the discretion of the surgeon, additional leads were implanted in adjacent levels if there was insufficient coverage of the pain region with the PRT effect. Negative PRT results were not considered exclusion criteria for a DRG trial.

For the trial period, one to three leads were placed using a minimally invasive epidural approach under general anaesthesia. No intraoperative paresthesia testing was done. Leads were anchored to the muscular fascia and were attached to an external trial stimulator using externalized extensions; stimulation was provided for three to seven days. At the end of trial, a new evaluation of the pain condition was performed using VAS. With a pain reduction of 50% and/or objective functional improvement of the patient, trial was considered successful and the implantation of the IPG was performed (Proclaim

DRG; Abbott Neurological, St. Jude Medical, Minneapolis, MN, USA). Patients with an increased surgical risk as well as patients with a clearly positive PRT result according to the experience of the responsible surgeon underwent all-in-one surgery. After the implantation of the complete neurostimulation system, the patient was interviewed in the regular out-patient visits within one week, as well as 1, 3, 6 and 12 months postoperatively using VAS, questionnaires and pain / paresthesia maps. The existence of paraesthesia in the previously painful area as well as the percentage of painful area covered with paraesthesia was documented. Patients with a pain relief of at least 50% under DRG stimulation were considered responsive.

All study elements were approved by the local ethics committee, and each patient gave written informed consent prior to the beginning of any study activities.

Results

Twenty patients with the indication for DRG stimulation were evaluated regarding pain development (Figure 11). Preoperative PRT was performed in all patients; no complications were observed. When results were not clear or incongruent with painful area, a second PRT was performed, and it was the case of 4 patients; for a congruent result, at least one PRT should be congruent. Overall, five patients were affected by CRPS, four patients by FBSS and most patients had another form of postsurgical neuropathic pain. Mean age was 54.8 years in the group; mean follow-up time was 10.9 months.

From overall 20 included patients, PRT was congruent with the pain region in 18 cases (90%). The two patients with incongruent results were however trialed for DRG because the pain region was clearly related to a very specific dermatome – one case did not achieve relevant pain relief during the trial and was later treated with an SCS; the other one was responsive during the trial and progressed to IPG implantation (patient 14). Because this single patient underwent an SCS, DRG stimulation was performed on 19 patients during this study.

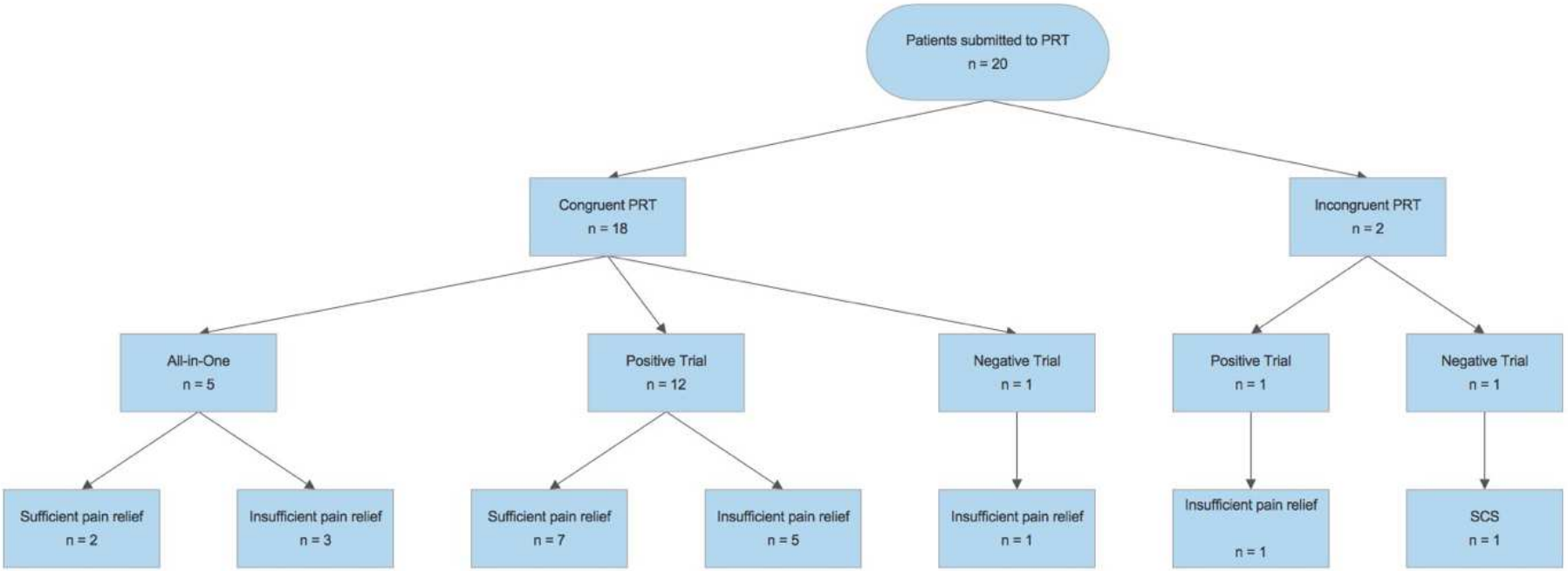

Fig. 1: Flow diagram of included subjects. This article is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), no changes were made (Sievert et al., 2021).

Table 3. PRT and DRG levels, clinical outcomes.

	Sex	Age	Diagnosis	PRT level	PRT congruence	DRG level	VAS Baseline	VAS 1 mo	VAS 3 mo	VAS 6 mo	VAS 12 mo	Coverage
1	M	58	FBSS	S1 left	+	S1 left	9	5	10	10	9 (0%)	30%
2	F	41	Pain after peripheral nerve injury	C6, C7 right	+	C6, C7 right	10	-	7	5 (-50%)	-	100%
3	F	27	FBSS	S1 left	+	S1 left	8	-	0	0	0 (-100%)	100%
4	F	52	CRPS I	C6 right	+	C6 right	7	5	7	6	7 (0%)	90%
5	F	29	CRPS II	L5 left	+	L5, S1 left	6	1	-	2	3 (-50%)	20%
6	M	56	Postarthroplasty	L3, L4 right	+	L2, L3, L4 right	5	5	7	4	2 (-60%)	100%
7	M	64	FBSS	L2 right	+	L2 right	7	7	7	1	3 (-57%)	-
8	M	44	CRPS II	L4 left	+	L4, L5, S1 left	10	-	9	10	9 (-10%)	-
9	M	42	CRPS II	L5 right	+	L5, S1 right	8	6	-	8	8 (0%)	50%
10	F	35	Postthoracotomy	Th11 right	+	Th9, Th10, Th11 right	8	5	5	3	2 (-75%)	100%
11	F	77	Postarthroplasty	L3, L4 right	+	L3, L4 right	8	9	8	4	3 (-63%)	-
12	M	68	Postarthroplasty	L3 right	+	L3, L4 right	3	2	6	-	6 (+50%)	0%
13	M	45	FBSS	S1 left	+	L5 left	9	-	-	-	7 (-22%)	-
14	M	80	Postarthroplasty	L3, L4 right	-	L3, L4 right	8	5	6	7	8 (0%)	-
15	F	51	Postsalpingectomy	Th12, L1 left	+	Th12, L1 left	9	7	9	-	9 (0%)	0%
16	M	69	Postarthroplasty	L3, L4 right	+	L3, L4 right	7	2	2	3	6 (-14%)	100%
17	M	82	Postarthroplasty	L2, L3 left	+	L2, L3 left	8	6	4	4	7 (-13%)	100%
18	F	49	Posttraumatic	S2 both	+	S2 both	9	0	1 (-89%)	-	-	-
19	M	79	Postherniotomy	L1, L2 right	+	L1, L2 right	10	0	0	5 (-50%)	-	-
20	F	49	CRPS I	Th9, Th12 right	-	None	8	-	-	-	-	-

Table 3: A second PRT was done in patients 1 (S1 left), 2 (C6 right), 10 (Th11 right) and 17 (L2 and L3 left). All-in-one procedures were the case of patients 5, 11, 12, 16 and 17. Implantation of a DRG lead in S1 was technically not possible in patient 13 due to fibrosis.

In the 18 patients with congruent PRT, five patients were selected for an all-in-one implantation at the discretion of the treating surgeon because the PRT yielded an adequate coverage of the painful area with a significant pain reduction. Out of this group, only two patients (40%) reported relevant sustained pain relief under DRG stimulation.

The remaining 13 patients with congruent PRT that were not considered for an all-in-one implantation were submitted to a trial; 12 patients had a positive trial. These subjects had a sustained significant pain relief under DRG stimulation in 53.8% of the cases in the last follow-up (7/13). The only with congruent PRT result but insufficient trial result was selected for the implantation of the IPG at discretion of the treating neurosurgeon for reasons that include significant functional improvement. No significant pain relief was achieved in this particular case. Considering now all patient groups, mean reduction in pain intensity under DRG stimulation was 31.7%; a total of 47.4% of the patients achieved sustained significant pain relief in the last follow-up (9/19).

In 11 patients, the trial leads were placed on the same level as previously tested positive by PRT (Table 3). In 6 patients, leads were placed in the PRT target and additionally in adjacent spinal levels, meaning that the PRT modified the original plan. In 15 patients, the leads were implanted on the same level as previously tested in the trial; in 2 patients, additional leads were implanted as a consequence of the trial results (patients 8 and 10) (Figure 12). In the particular case of patient 13, the implantation of a DRG lead in S1 was technically not possible because of fibrosis, and the patient had a lead in L5 implanted.

Data to coverage of the painful area with paraesthesia was available for 12 patients, all of them with a previous congruent PRT result. Two thirds of them reported a coverage of the target area of at least 50%. For the six patients with

additional implanted leads as a consequence of the PRT results (patients 2, 5, 6, 8, 9 and 10), 80% achieved a coverage of at least 50%, with data being unavailable for patient 8.

A total of 7 patients underwent revision surgery, which included broken leads and lead defect, among other causes. One patient died before the end of the study unrelated to the DRG system or surgery, the remaining 18 implanted patients were observed over a period of 12 months.

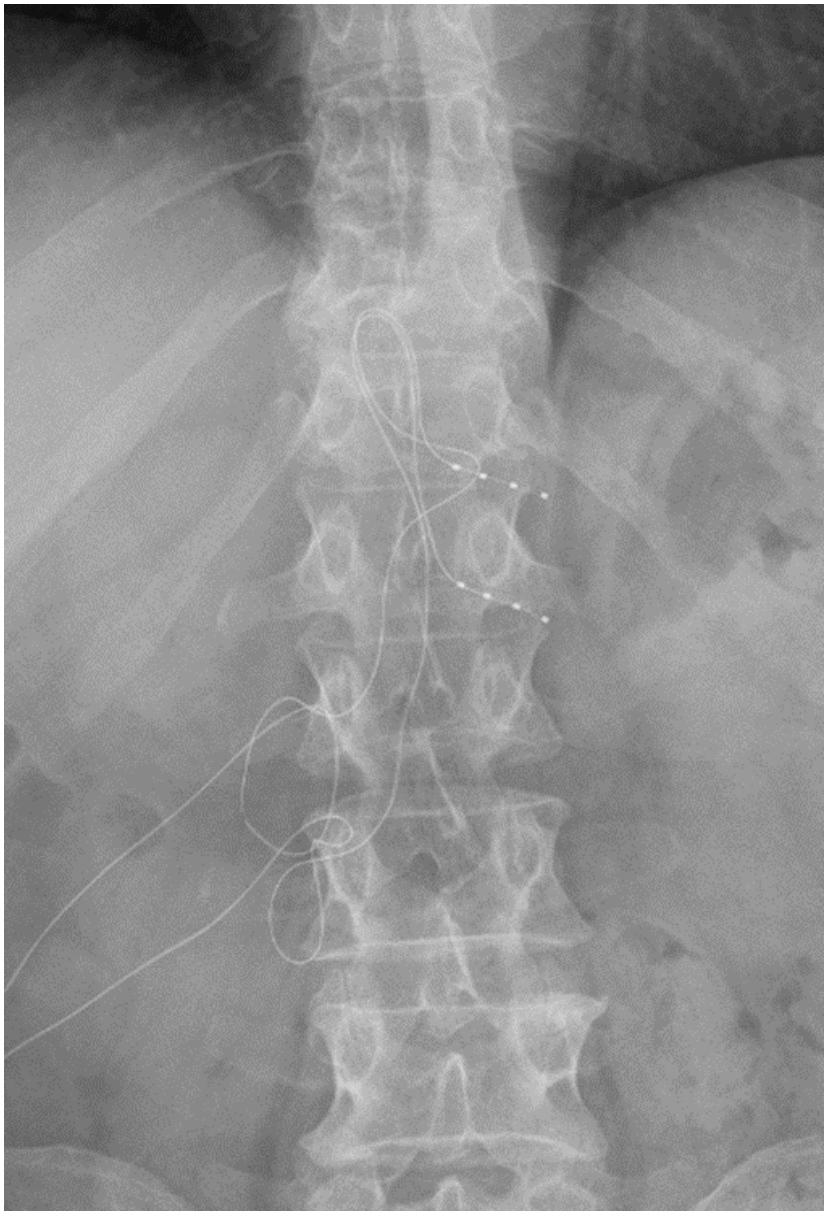

Fig. 12: DRG leads in Th12 and L1, the patient suffered from chronic pain after a salpingectomy. This article is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), no changes were made (Sievert et al., 2021).

Discussion

The aim of the study was to investigate whether the preoperative periradicular therapy is eligible in a preoperative protocol for identifying the correct spinal level for DRG stimulation regarding the coverage of the painful area with stimulation-induced paresthesia. Compared to the past case studies on methods for predicting targets for DRG stimulation by Zuidema et al. (Zuidema et al., 2014) on retrograde transforaminal paresthesia mapping, with 3 patients with groin pain, and by Hunter et al. on radiofrequency stimulation, with 4 patients with postamputation pain of the lower extremity (Hunter et al., 2017), a considerably larger number of patients could be examined. Similarly, the selection of patients investigated in this study was not limited to an underlying disease or localization of pain. The study thus provides a good representative picture of the patient population of neuropathic pain. In comparison to the mentioned studies, the present study enabled an analysis of a longer-term stimulation result after successful PRT testing.

In our department, PRT has become standard of care in almost all patients being screened for DRG for confirmation of the target level. Bupivacaine is usually preferred and has a longer elimination half-life than lidocaine. Lead implantation occurs on the following day, so that no analgesic effect of the PRT should be present. In this study, however, all lead implantations were done under general anaesthesia without paresthesia control. Even when the initial PRT does not cover the entire painful area, it orientates the surgeon when choosing the target DRG. If the first PRT result is not congruent with the painful area, a second PRT may be helpful, which was the case of three patients in this study. In case of insufficient coverage after PRT, the direct implantation of another lead in the trial without prior testing becomes more justifiable when a first PRT confirmed at least partial improvement. As a single-arm study, no comparisons can be made with the coverage rates of a control group that did not undergo a preoperative PRT. Our study was, however, able to show that the PRT results modified the original targets established by the responsible surgeons based on anatomical landmarks in a considerable number of patients. It is true that insufficient coverage can also be detected in the trial phase, but the preoperative PRT turns

the trial into a second opportunity to evaluate the adequate coverage of the painful area before implantation of the definitive system. Unfortunately, we did not find any references regarding the incidence of second or even third procedures for the implantation of new DRG leads after the implantation of the IPG because of insufficient pain coverage. It is intuitive, however, that a preoperative PRT could reduce the length of hospital stay and the risks of new surgical procedures because more affected levels are earlier identified additionally to the clinically inferred ones. It might offer additional option to reconsider the neuromodulation strategy for every individual patient. In this study with 19 subjects submitted to DRG stimulation, a second operation for implantation of new leads did not occur.

Not as intuitive is the possible predictive value of preoperative PRT over the outcomes of DRG stimulation. These therapies have different mechanisms of action, but such a relationship would be of considerable interest, as it might indicate which patients would not benefit from DRG stimulation – whose technique for lead placement is particularly more difficult when compared with traditional spinal cord stimulation. For a matter of comparison, the positive predictive value of a successful trial for sustained significant pain relief achieved 53.8% in this study. As only one patient had a negative trial and was submitted to DRG stimulation later, nothing can be said about its negative predictive value based on these data.

Particularly interesting is the case of the five patients submitted to an all-in-one implantation of DRG leads following a very successful PRT testing. In these cases, when PRT results were most promising considering adequate coverage and reduction of pain intensity, the positive predictive value for final significant pain relief was only 40% and 50% for coverage of at least 50% of the painful area. This result regarding pain reduction is lower than the predictive value of a trial (53.8%), which remains as gold standard for the selection of patients for implantation of the definitive system. The predictive value regarding coverage of the painful area was also lower than the value obtained considering all 12 patients with available coverage data (67%). The indication for an all-in-one implantation of DRG leads is given at discretion of the responsible surgeon

and should be specially considered in patients with higher surgical risk, but data of this study with a limited sample size supports a stepwise approach with a stimulation trial – independent of how promising PRT results are.

Limitations

This study evaluated only the congruence of PRT effect with the painful area and not the effect of PRT over the pain intensity. No conclusions can be drawn regarding its predictive value to stimulation outcomes. It is however relevant to mention that the variability of PRT results is influenced by physician experience and technical aspects, such as anaesthetics used and addition of steroids. Therefore, insufficient pain relief after PRT would not change our indication for a DRG trial, as it was the case with patient 14. The inclusion of PRT in our clinical routine is independent of its positive predictive value over final clinical outcomes.

Conclusion

The success of the DRG stimulation depends on the correct lead placement and PRT is a helpful tool to confirm the stimulation targets. A PRT preceding the stimulation trial represents an additional opportunity to optimize the coverage of the target area with stimulation-induced paresthesia for patients operated under general anesthesia.

6 Frequency dependency of therapeutic efficacy in dorsal root ganglion stimulation for neuropathic pain

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Introduction

Dorsal root ganglion (DRG) stimulation has been effectively used in the treatment of neuropathic pain of different etiologies. In neuropathic pain, spontaneous firing as a consequence of lower action potential thresholds can be observed in the DRG neurons (Koopmeiners et al., 2013). Different stimulation frequencies could lower this abnormal activity with different intensities by readjusting the action potential threshold. In a traditional view of “stimulation dose”, patients requiring more pain relief would respond to a higher total electrical energy delivery, which is dependent on current, pulse width and stimulation frequency (Miller et al., 2016). However, recent studies have shown that DRG-S with lower frequencies – and therefore with lower total energy delivery – could be an effective alternative. A sub-analysis of the ACCURATE study (Deer et al., 2017) reported paresthesia-free subjects using DRG-S that achieved similar pain relief with lower amplitudes and frequencies (Mekhail et al., 2020a). Koetsier et al. were able to show a delayed wash-out effect of DRG-S in the treatment of painful diabetic neuropathy in rats (Koetsier et al., 2020). Chapman et al. reported a case series with tapering of stimulation frequencies in twenty patients with refractory back pain down to 4 Hz and reported sustained pain relief (Chapman et al., 2020b).

It is assumed that specific neural components of the DRG can be influenced in a targeted manner by the selection of different frequencies and that different pain patterns can be optimally treated with different frequencies. Little is known about the effect of stimulation frequency over the clinical outcomes of

DRG-S. We report on the first randomized double-blind clinical trial testing mid-frequency DRG-S in patients with neuropathic pain.

Material and methods

Patients aged above 18 years old with a DRG stimulation system implanted and followed-up at the Department of Neurosurgery of the Heinrich-Heine-University Düsseldorf were invited to participate in the study. Written informed consent was obtained. Individuals were excluded from the trial in case of further significant pain that might confound the study assessments. Nineteen patients participated in the study. The study was approved by the Ethics Committee of the Medical Faculty under the number 2020-1120 and was registered at the German Clinical Trials Register (DRKS) under DRKS00022557.

Patients were evaluated for neuropathic pain with PainDetect (0-38 points) at the baseline. All patients tested five different stimulation parameter settings in a randomized order: stimulation frequencies of 20 Hz, 40 Hz, 60 Hz, 80 Hz and sham stimulation. Sham means amplitude set at 0.025 mA, the minimum amplitude allowed, so that the IPG indicates to the patient stimulation on, but delivers only ineffective stimulation. Patients were programmed at subthreshold for each tested frequency, amplitude was corrected in each case. Patients and investigators were blinded, a study nurse had access to unblinded data. Each stimulation parameter setting was tested for four days and was followed by a two-day washout period. The stimulation parameters were programmed in advance by a study nurse and were randomly changed by the patients each week at home. The stimulation amplitude was programmed to subthreshold levels individually for each frequency. At the end of each phase, the patients were interviewed by phone and completed numbered questionnaires.

At baseline, VAS and clinical parameters were assessed, pre DRG-S pain data was collected from charts. During the study patients underwent assessment of pain intensity and quality using the visual analogue scale and McGill Pain Questionnaire (MPQ, 0-78 points), of quality of life using EQ-5D (Index 0-1), and of the prevalence of depression using the Beck Depression Inventory (BDI, 0-63 points). Any additional intake of analgesics was documented by the patients.

Statistical analysis

Patients' demographics were analyzed using descriptive statistics and presented as frequency and percentage for categorical variables, and as numbers, means, minima, maxima and standard deviations (SD) for continuous variables. Statistical analysis was performed using SPSS 19 software (IBM Cooperation, USA) and GraphPad Prism 8.0.2.

Repeated measurement one-way ANOVA was used for comparison between baseline data and measurements at the different frequency settings applying Tukey´s multiple comparison test. An alpha error of 0.05 was considered significant, 0.01 was considered highly significant.

Results

A total number of 19 patients participated in the study. The mean age was 53 years (range: 25-80) and the patients were using DRG-S for a mean of 17.2 months (range: 4-102). The most common pain etiology was chronic regional pain syndrome (CRPS) (7 subjects), followed by postsurgical pain after implantation of joint prosthesis (4), post-herpetic neuralgia (3), nerve injury after resection of neurinomas (2), traumatic nerve injury (2) and diabetic polyneuropathy (1). Fourteen patients had a PainDetect Score of 12 or higher (76.7%), indicating higher probability of neuropathic pain. Patients reported a mean VAS of 8.6 (SD 1.0) before the implantation of the DRG-S system and a mean baseline VAS of 3.9 (SD 1.9). All patients had already been programmed in the clinical routine and had reached a stable therapeutic response. All patients had a stimulation frequency of 20 Hz at study start.

Even at subthreshold level with corrected amplitude, some patients experienced at higher frequencies a change in the paresthesia field. Amplitude was reduced in these cases. No patient had painful paresthesia nor motor stimulation.

Table 4. Pain intensity under different stimulation frequencies.

No.	Age	Pain etiology	PainDetect	VAS pre DRG-S	VAS baseline	VAS 20 Hz	VAS 40 Hz	VAS 60 Hz	VAS 80 Hz	VAS Sham
1	26	Postherpetic neuralgia	17	8	4	4	8	6	4	8
2	59	CRPS	9	9	7	5	7	7	7	8
3	59	Postsurgical after implantation of joint prothesis	19	10	5	4	4	5	6	10
4	38	Nerve injury after neuroma resection	12	8	3	2	3	2	2	8
5	60	Postsurgical after implantation of joint prothesis	19	8	2	2	3	4	4	7
6	53	Postherpetic neuralgia	5	8	0	0	2	4	4	6
7	35	CRPS	24	9	3	3	1	9	7	9
8	70	Postherpetic neuralgia	19	8	1	2	5	8	8	8
9	65	Postsurgical after implantation of joint prothesis	14	8	5	5	7	8	8	9
10	80	CRPS	9	8	3	3	3	4	5	7
11	71	Traumatic nerve injury	9	8	3	3	4	5	5	7
12	40	CRPS	32	10	6	7	8	8	8	10
13	56	CRPS	13	8	4	3	7	7	9	9
14	35	CRPS	34	10	5	4	7	7	5	10
15	74	Diabetic polyneuropathy	15	6	4	3	4	5	4	10
16	48	Postsurgical after herniotomy	12	9	7	7	7	5	5	8
17	25	CRPS	20	9	7	7	7	6	8	9
18	50	Nerve injury after neuroma resection	16	10	4	5	4	8	7	10
19	55	Postsurgical after implantation of joint prothesis	7	9	2	2	3	4	4	10
		Mean (SD)	16 (7.9)	8.57 (1.01)	3.94 (1.98)	3.73 (1.91)	4.94 (2.19)	5.89 (1.88)	5.78 (1.93)	8.57 (1.26)

Table 4: Pain intensity under stimulation frequencies of 20 Hz, 40 Hz, 60 Hz, 80 Hz and sham stimulation. This article is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), no changes were made (Piedade et al., 2022).

Results for mean VAS for 20 Hz, 40 Hz, 60 Hz, 80 Hz and sham stimulation were 3.7 (SD 1.9), 4.9 (SD 2.2), 5.8 (SD 1.9), 5.8 (SD 1.9) and 8.6 (SD 1.3) respectively (Table 4). 20 Hz achieved significantly lower pain intensity than 40 Hz ($p = 0.004$) and any other tested stimulation parameters ($p < 0.001$). 40 Hz did not result in significantly better results than 60 Hz ($p = 0.086$), nor did 60 Hz have lower pain intensities than 80 Hz ($p = 0.695$) (Figure 13). Although the overall trend and statistics favor lower stimulation frequencies, two patients preferred higher stimulation frequencies and reported better pain control. In both cases amplitude remained at the necessary level for subthreshold stimulation.

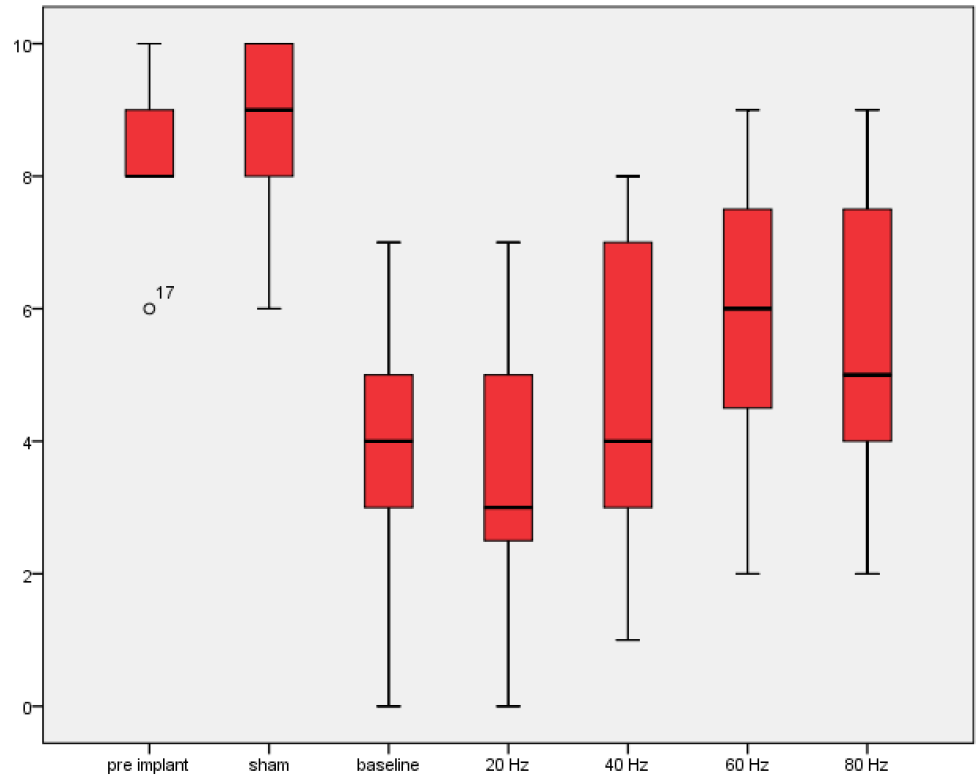

Fig. 13: Mean VAS pre DRG-S, under sham stimulation, at baseline and under 20, 40, 60 and 80 Hz. This article is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), no changes were made (Piedade et al., 2022).

The same trend was seen with the McGill Pain Questionnaire, which resulted in 30.8 (SD 15.8), 33.1 (SD 17.3), 35.9 (SD 16.9), 36.3 (SD 14.2) and 46.5 (SD 17.2) points. In this case, statistical significance was only achieved when comparing MPQ results of 20 Hz and 80 Hz ($p = 0.047$).

When analyzing quality of life, EQ-5D indexes were 0.76 (SD 0.16), 0.69 (SD 0.26), 0.59 (SD 0.30), 0.58 (SD 0.30) and 0.24 (SD 0.37). The index for 20 Hz was not significantly higher than for 40 Hz ($p = 0.071$), but than for 60 Hz and 80 Hz ($p = 0.001$).

Beck Depression Inventory resulted for the same groups 9.9 (SD 7.8), 10.8 (SD 7.1), 11.9 (SD 8.9), 13.6 (SD 8.7) and 15.5 (SD 10.2) points. Under 20 Hz, BDI was not significantly lower than under 40 Hz ($p = 0.19$), but under 60 Hz ($p = 0.033$) and 80 Hz ($p = 0.005$). Table 5 shows comprehensive data with the mean difference and statistical significance.

Although only assessed in a very basic fashion (increase in medication yes/no), the lowest number of patients reported an increased need for analgesic medication during 20 Hz stimulation (9 subjects), 13 patients referred increased analgesics intake during 40 Hz stimulation, 16 subjects under 60 Hz and 80 Hz, whereas all 19 patients reported an increase during sham stimulation.

When stratified by PainDetect, a higher overall VAS and a higher mean difference in the VAS between stimulation frequencies was observed in the patients with a score >12 without reaching statistical significance. The overall observation regarding better pain control with lower frequencies was still observed.

Discussion

Dorsal root ganglion stimulation is an effective form of treatment for chronic, especially neuropathic, pain conditions. The choice of stimulation frequency shows a clear influence on pain reduction and the associated quality of life. Lower stimulation frequencies seem to be most effective in the examined pain etiologies, which is explained by the pathophysiology of pain processing.

Table 5. Mean difference between baseline data and treatment groups adjusted with Tukey's multiple comparison.

		pre DRG-S	Baseline	20 Hz	40 Hz	60 Hz	80 Hz	sham
pre DRG-S	VAS		4.632 (**)	4.842 (**)	3.632 (**)	2.684 (**)	2.789 (**)	0.000 (n.s.)
	MGPQ							
	EQ5D							
	BDI							
Baseline	VAS	4.632 (**)		0,210 (n.s.)	-1.000 (n.s.)	-1.947 (*)	- 1.842 (*)	-4.632 (**)
	MGPQ							
	EQ5D							
	BDI							
20 Hz	VAS	4.842 (**)	0,210 (n.s.)		-1.211 (*)	-2.158 (**)	-2.053 (**)	-4.842 (**)
	MGPQ				-2.263 (n.s.)	-5.053 (n.s.)	-5.474 (*)	-15.68 (*)
	EQ5D				0.07495 (n.s.)	0.1702 (*)	0.1733 (*)	0.5187 (*)
	BDI				-0.8947 (n.s.)	-2.053 (n.s.)	-3.684 (*)	-5579 (**)
40 Hz	VAS	3.632 (**)	-1.000 (n.s.)	-1.211 (*)		-0.9474 (n.s.)	-0.8421 (n.s.)	-3.632 (**)
	MGPQ			-2.263 (n.s.)		-2.789 (n.s.)	-3.211 (n.s.)	-13.42 (*)
	EQ5D			0.07495 (n.s.)		0.09526 (n.s.)	0.09837 (n.s.)	0.4438 (*)
	BDI			-0.8947 (n.s.)		-1.158 (n.s.)	-2.789 (n.s.)	-4.684 (*)
60 Hz	VAS	2.684 (**)	-1.947 (*)	-2.158 (**)	-0.9474 (n.s.)		0.1053 (n.s.)	-2.684 (**)
	MGPQ			-5.053 (n.s.)	-2.789 (n.s.)		-0.4211 (n.s.)	-10.63 (*)
	EQ5D			0.1702 (*)	0.09526 (n.s.)		0.0031 (n.s.)	0.3485 (*)
	BDI			-2.053 (n.s.)	-1.158 (n.s.)		-1.632 (n.s.)	-3.526 (n.s.)
80 Hz	VAS	2.789 (**)	- 1.842 (*)	-2.053 (**)	-0.8421 (n.s.)	0.1053 (n.s.)		-2.789 (**)
	MGPQ			-5.474 (*)	-3.211 (n.s.)	-0.4211 (n.s.)		-10.21 (*)
	EQ5D			0.1733 (*)	0.09837 (n.s.)	0.0031 (n.s.)		0.3454 (*)
	BDI			-3.684 (*)	-2.789 (n.s.)	-1.632 (n.s.)		-1.895 (n.s.)
sham	VAS	0.000 (n.s.)	-4.632 (**)	-4.842 (**)	-3.632 (**)	-2.684 (**)	-2.789 (**)	
	MGPQ			-15.68 (*)	-13.42 (*)	-10.63 (*)	-10.21 (*)	
	EQ5D			0.5187 (*)	0.4438 (*)	0.3485 (*)	0.3454 (*)	
	BDI			-5579 (**)	-4.684 (*)	-3.526 (n.s.)	-1.895 (n.s.)	

Table 5: No EQ5D, BDI and MGPQ data is available at baseline and only VAS data is available pre DRG-S implantation. *: significant (< 0.05), **: highly significant (< 0.01), n.s.: not significant.

A possible mechanism of action of DRG-S involves the activation of low-threshold mechanoreceptors, which are Aß-, Aδ- and C-fiber afferents transmitting fine touch sensation. These fibers play an important role also inhibiting painful stimuli at the level of the dorsal horn (Habig et al., 2017). Animal studies in vitro showed that high- and low-frequency DRG stimulation act over different inhibitory pathways in rats. Whereas low-frequency stimulation of 0.2-1.0 Hz promoted a pain relief that was suspended with naloxone, the effect of high-frequency stimulation of 100 Hz was reversed with GABA and glycine antagonists in transverse slices of rat spinal cords (Ikeda et al., 2000, 1999; Sandkühler et al., 1997). The different roles of high- and low-frequency DRG stimulation have not been investigated in humans so far.

The reason why low- and high-frequency stimulation may work differently is probably the phase locking of low-threshold mechanoreceptors. This occurs when neurons fire at the same frequency as the stimulation and it is only possible at certain stimulation frequencies depending on neurophysiological properties of each fiber. As shown by Arcourt et al. in a study with optogenetically modified rats, low-threshold mechanoreceptors in these animals were subject to phase locking for frequencies up to 20 Hz, after which neurons start asynchronous firing (Arcourt et al., 2017). Assuming similar properties in the human population, for which such physiological studies lack, phase locking could be an explanation for the findings of the present study – the first of its type, to the best of our knowledge –, with most patients reporting higher pain intensities under higher stimulation frequencies.

The frequency effect was less evident in patients with a PainDetect score under 12, which indicates a less pronounced neuropathic component in the overall pain. Dichotomizing the group by the PainDetect score did not result in a statistically significant difference but in a trend. This study might simply be

underpowered to clearly reveal this difference. These subjects with an important nociceptive pain, which did also benefit from DRG-S in this trial like patients with classic neuropathic pain, seem not to rely exclusively on the endogenous intraspinal opioid inhibitory pathway for pain relief. This interesting finding is yet to be confirmed with further studies and could help extending neuromodulation for the much larger population with nociceptive pain.

In our study, we used a two-day washout period. In most patients, DRG-S elicits fast to immediate response regarding pain control, but some effects of DRG-S go beyond pain control, e.g. autonomic symptoms in CRPS. These commonly take longer to become effective and are therefore likely underestimated in this study. For studies investigating only pain control, the washout period could even be shortened. In studies investigating autonomic effects, the stimulation interval and washout periods should be extended. This is especially important in studies looking into the efficacy of neuromodulation to modulate the function of immune system e.g. to treat CRPS, osteoarthritis and similar disorders (Gravius et al., 2019).

This trial is the first to investigate the influence of stimulation frequencies in DRG-S in a double-blind, randomized, prospective setting. We tested frequencies down to 20 Hz – a mid-frequency stimulation. We recognize the potential of even lower stimulation frequencies down to 4 Hz, as shown by Chapman in his important case series (Chapman et al., 2020b). We are currently further investigating the influence of stimulation frequency in DRG-S with the aim to predict optimal stimulation frequencies based in the underlying condition and the proportion of neuropathic and nociceptive pain. The relevance of such studies goes far beyond the expected elongation of battery lifetime, the focus is the targeted approach of different nerve fibers with unique neurophysiological properties. Additionally, stimulation with lower intensities and less energy-transfer is thought to induce less habituation preventing loss of effect over time (Levy et al., 2020).

Limitations

The study results are limited by the fact that all the subjects were using 20

Hz of stimulation frequency for a long time prior to study begin.

Conclusions

The choice of the stimulation frequency shows a clear influence on the pain reduction and the associated well-being and quality of life of the patient. Lower stimulation frequencies seem to be most effective for neuropathic pain. As soon as larger similar studies are available, conclusions will be drawn regarding the functioning of the DRG in different pain etiologies and the pathophysiology of pain processing.

7 Discussion

7.1 Extending the access to dorsal root ganglion stimulation

Unfavorable anatomy prevented many patients from the placement of DRG leads using the classical percutaneous implantation technique. Conditions such as previous laminectomy, foraminal stenosis, unforeseen structural adhesions and even previous DRG-S pose a challenge for the correct insertion of a lead in the neuroforamen. The first description of an open implantation technique in the literature was provided in the publication “Open microsurgical dorsal root ganglion lead placement” (Guilherme S. Piedade et al., 2019). Surgical access to the neuroforamen is a standard neurosurgical procedure, the real challenge of an open implantation technique is the lead fixation to avoid future dislocations. This is achieved by the percutaneous technique with the posterior bone layer of the lamina, which must be resected in an open procedure. Beyond technical aspects of lead insertion in the neuroforamen, the most important contribution of this work is perhaps the description of strain relief loops and fibrin glue as adequate resources for stabilization of lead position. The cranial portion of the loops was also placed under the remaining cranial lamina to increase stability. No lead dislocation was present at 12- and 18-month follow-up.

The open lead placement technique was later again described with modifications by Johnson and Seibly for the treatment of a patient with postherpetic neuralgia and neuropathic pain in the dermatomes T9-12 left. The patient’s history included an intrathecal analgesia pump, percutaneous and paddle SCS leads. A trial of DRG-S was attempted but no lead could be placed due to extensive epidural scarring. In this case, laminectomies were performed from T8 to T12. The fixation of the leads was achieved with plastic anchors to the fascia and scar tissue at the levels T9-10 and with titanium cranial fixation plates and screws over the contralateral rest of the laminae at the levels T11-12. No

epidural strain relief loops were used. No dislocations occurred after six months (Johnson and Seibly, 2021).

Another possibility for the placement of lumbar DRG leads was first developed by Al-Kaisy and called transgrade percutaneous approach (Al-Kaisy et al., 2019). It differs from the classical anterograde approach (Deer et al., 2019c) in that the entry point for the Tuohy needle should be at the vertebral level above and not below the target foramen. Case series were published with success for patients with previous laminectomy or DRG-S (Chapman et al., 2020a; Smith et al., 2021). Although useful in lumbar spine, the overlapping laminae at each thoracic and cervical vertebral level render this technique inappropriate for these spinal segments.

When the transgrade approach is considered, the open placement of DRG leads seems appropriate for foraminal pathologies, thoracic lead implantation or extensive epidural scarring with the need to implant multiple DRG leads in the correspondent area. The transgrade approach may be the best option for smaller scarring areas and for the placement of fewer DRG leads in the lumbar spine. However, more patients need to be studied to reach a more definitive conclusion about the value of these techniques.

Similar to patients with significant anatomical barriers for lead implantation, subjects with neuropathic pain in the upper extremities were for some time excluded from neuromodulation of the DRG in its modern phase. Curiously, one of the first reports of DRG-S, still with SCS lead, was the case of stimulation of the C2 DRG for postherpetic neuralgia (Lynch et al., 2011). The publication “Cervical and high-thoracic dorsal root ganglion stimulation in chronic neuropathic pain” has the merit to expose the technical aspects and the outcomes of DRG-S in a very large group of patients, which performed similar to the subjects treated for neuropathic pain of the lower extremities with DRG-S (Guilherme Santos Piedade et al., 2019). Etiologies affecting almost exclusively the upper extremities und the high-thoracic region, such as intercostal neuralgia and postherpetic neuralgia, are now addressed with DRG-S. This publication has also the particularity of describing for the first time the use of DRG-S for pain following the resection of an intramedullary spinal tumor. Few other cases of

cervical DRG-S were later described in the literature, majorly following traumatic peripheral nerve injury (Kretzschmar et al., 2021), but evidence remains still very limited. It is important to point out that the effect of stimulation in cervical levels is movement-dependent, in contrast to stimulation of lumbar roots. Although stimulation of cervical DRGs is feasible and safe, the risks of spinal cord injury are much higher above C4. When higher cervical roots need treatment, the paramedian placement of an SCS lead is much safer and seems to have a comparable benefit.

DRG-S may not only be an appropriate first surgical treatment for neuropathic pain, but also an adequate add-on therapy for complex cases that failed to SCS. The publication “Synergetic efficacy of simultaneous DRG- and traditional spinal cord stimulation” clarifies the role of DRG-S simultaneous to a preexisting SCS system. Patients who failed SCS because of inadequate coverage of the painful region or because of exacerbation of another secondary pain component may benefit from DRG-S (Piedade et al., 2020). Two other cases of DRG-S performed in SCS failure were reported by Yang and Hunter, but in both patients with CRPS there was no second pain component nor coverage problems – the positive response to SCS diminished over time, which is already described in the literature (Atkinson et al., 2011). In one case, the SCS system was substituted for DRG-S with success. In the second one, the patient remained with both DRG-S and SCS implanted but preferred only the DRG-S system activated (Yang and Hunter, 2017). Although simultaneous stimulation was not desired, this important publication complements the concept of DRG-S as add-on therapy.

7.2 Choosing the target level

Choosing the appropriate target DRG is essential for adequate coverage of the painful area and therefore pain relief. Each DRG is classically responsible for the sensibility of a single dermatome, the distribution of dermatomes in patients normally corresponds to their traditional representation in the literature. The anatomical mapping belongs to the physical examination of every patient

evaluated for DRG-S, but it does not always give the correct spinal levels accurately. Even though the DRG is a very organized structure with a somatotopic arrangement (Puigdellívol-Sánchez et al., 1998), neurons from different DRGs may synapse in the same spinal location, what is called convergent pathway. Similarly, the same neuron of a DRG may connect with different targets in the spine, forming divergent pathways (Pinto et al., 2010).

The DRG-S was originally designed to be performed in awake patients with intraoperative paresthesia testing – the gold standard, because it confirms the target level, assesses the coverage of the painful area and indicates incorrect lead position in the case of motor stimulation. This procedure is, however, somehow complex because patients need sedation during the painful lead insertion in the neuroforamen. Patients may accidently move during surgery and may need to be awakened several times, this is time-consuming and for some patients very inconvenient. As an alternative, Zuidema et al. used a radiofrequency generator in three patients to stimulate multiple DRGs preoperatively and map the elicited paresthesia, obtaining adequate coverage after implantation of the definitive DRG-S system (Zuidema et al., 2014). Hunter et al. applied selective radiofrequency in four cases to test different DRGs in postamputation pain, when no dermatome can be evaluated (Hunter et al., 2017). Preoperative mapping with radiofrequency is currently used in some centers.

The publication “The role of periradicular infiltration in dorsal root ganglion stimulation for chronic neuropathic pain” discusses prospective data of 20 patients to propose the PRT as a standard preoperative investigation tool to confirm the target level prior to a stimulation trial. As a single-arm study without a control group, no comparisons could be made with intraoperative testing in awake patients regarding adequate coverage or clinical outcomes. In this study, however, PRT results modified in many patients the original targets determined anatomically (Sievert et al., 2021). The adoption of PRT or mapping with radiofrequency in the clinical routine enables the performance of DRG-S under general anesthesia, a huge advantage for many patients with chronic pain and mental comorbidities.

The choice between preoperative mapping or PRT test considers mostly the local structure of each facility. When compared to the PRT, mapping with a radiofrequency generator assesses the coverage of the painful area and additionally the response to stimulation. There are no studies documenting the predictive value of a mapping over clinical outcomes, but it is expected that stimulation of the DRGs with a radiofrequency needle will elicit the same effect of the implanted lead because the mechanism of action is the same – even when the preoperative mapping lasts only for some minutes. The PRT, however, is not adequate to predict response to stimulation and can solely identify the correct anatomical target. It must also be considered that a PRT done with excessive volume of anesthetics will affect neighboring DRGs too as the medication spreads in the epidural space. The PRT test is certainly an adequate preoperative assessment, but the mapping with a radiofrequency generator is more complete and could potentially predict response to therapy. As a radiofrequency mapping requires more structure from an implanting center, however, the PRT test is often preferred.

Although most of the cases require the identification of a specific level for the treatment of a focal neuropathic pain, diseases like phantom limb pain and postherpetic neuralgia hardly fit in this concept and may pose real challenges to the physician. The best strategy in postamputation pain is to start the preoperative test – PRT or radiofrequency mapping – with the dermatome where the pain started according to the patient. Stimulation of multiple DRGs to cover the entire extremity is rarely necessary. Neuromodulation for postherpetic neuralgia is a potentially polemical issue, this disease affects classically the DRG itself and stimulation of the affected level may therefore not be forwarded to the spine. In this case, levels above and below may be targeted considering the existence of convergent and divergent pathways. Even if DRG-S is not always successful in this pathology, satisfactory results may be achieved in selected patients.

7.3 Programming in dorsal root ganglion stimulation

Whereas different frequencies and waveforms were extensively studies in SCS, little was known about the effect of frequency over the clinical outcomes in DRG-S. There was evidence that lower frequencies could be advantageous in animal studies (Koetsier et al., 2020), Chapman et al. reported an unblinded case series of patients being programmed down to frequencies as low as 4 Hz (Chapman et al., 2020b). The publication “Frequency dependency of therapeutic efficacy in dorsal root ganglion stimulation for neuropathic pain” brings the first randomized, controlled, double-blind clinical trial examining the influence of different stimulation frequencies in the range from 20 to 80 Hz (Piedade et al., 2022). Data favored lower stimulation frequencies, as supported by the theory of phase locking of low-threshold mechanoreceptors (Arcourt et al., 2017).

These findings are highly dependent on electrophysiological properties of the target fibers. Although the stimulation of low-threshold mechanoreceptors is important in the mechanism of DRG-S, these are probably not the only fibers whose functioning is influenced by stimulation. Different neurons – with different electrophysiological properties – may play a more important role in selected diseases. The role of low-threshold mechanoreceptors is established in the stimulation for chronic neuropathic pain, but has not been studied in the setting of acute or nociceptive pain. This first clinical trial reflects the findings of previous non-controlled studies but by no means ends the discussion on stimulation frequency in DRG-S. The effect of even lower frequencies is subject of clinical trials running at the moment.

One relevant economical consequence of this clinical trial is to save battery lifetime of the IPGs. Since stimulation frequency is the single most important factor determining the lifetime of the devices, a frequency reduction may reduce the costs of healthcare systems with the replacement of non-rechargeable IPGs or even encourage companies to produce smaller implantable devices. Another strategy that could save battery lifetime includes cycling of stimulation, which would not be delivered continuously, but rather intercalated with pauses. Chapman et al. examined pauses of up to two minutes following one

minute of stimulation, there were no significant changes in pain scores compared with continuous stimulation (Chapman et al., 2021).

7.4 Future of dorsal root ganglion stimulation

DRG-S emerged after the publication of the ACCURATE trial. Curiously, DRG-S was named in the title of this trial “spinal cord stimulation of the dorsal root ganglion”. Over time, DRG-S evolved as an independent therapy with its own name because the DRG was recognized as a unique stimulation target, its electrophysiological characteristics and its particular anatomy delimit and separate DRG-S from SCS. New concepts and technical developments will continue to shape the DRG-S of the future.

The use of DRG-S in the cervical spine should be encouraged because it allows the treatment of diseases rarely affecting the lower limbs. Currently, DRG leads may be implanted in the U.S. up to T10 and in Europe in every spinal level, however hardly going higher than C4 because of the risk of injury to the cervical spinal cord. Very familiar to neurosurgeons, neuronavigation in the spine in generally used to improve the placement of pedicle screws, but could also offer additional safety to lead implantation in the cervical spine. It requires an intraoperative CT scan of the spine marked with a reference clamp or pin and provides a tridimensional anatomical map that can be navigated by the surgeon. This established method has not been described in the setting of DRG-S yet, but could potentially reduce the risks of spinal cord injury and optimize lead position in the dorsosuperior portion of the neuroforamen.

The value of such a technique must be critically discussed. It indeed can provide more safety for cervical cases, but it is unclear whether levels higher than C4 would become a target for DRG leads. The C1 root typically has no sensory component and therefore no dermatome, but targeting the C2 DRG could potentially address diseases like occipital neuralgia and, due to the relationship with the trigeminocervical complex in the spine, migraine and cluster headache. These conditions are currently treated with occipital nerve stimulation, a technique with high complication rate because the leads pass through very

mobile articulations along the neck. Although still subject to the rotation of C1 over C2, a bilateral C2 DRG-S would be exposed to less movement stress. The risks, however, of nerve or vascular injury in occipital nerve stimulation are almost inexistent. If neuronavigation provides enough safety to stimulate higher cervical levels, DRG-S could become a tool in the treatment of chronic facial pain.

The programming in DRG-S should experience a revolution in the next few years. After documentation of higher efficacy with stimulation frequencies as low as 20 Hz, many clinical trials are expected to test even lower settings. However, the key advance in the field will probably not be the discovery of a specific frequency with ideal effect in DRG-S, but rather the identification of frequency ranges to which different diseases – an even disease stages – better respond. The case of CRPS is very illustrative because this condition affects C fibers, causing important autonomic symptoms. There have been no such studies with sufficient sample size so far, but maybe it could be shown in the future that relief of autonomic symptoms is better achieved with a frequency targeting C fibers, whereas pain relief responds better to frequencies addressing low-threshold mechanoreceptors. Stimulation frequency is the key to target different types neural fibers because of their unique electrophysiological properties. There must be also a difference between stimulation for chronic pain that lasts for some years and for pain that lasts for some decades. Intense pain leads to central sensitization and cortical reorganization after many years (Maihöfner et al., 2003), so that the target for stimulation in patients with long-lasting chronic pain may become other fibers connecting with specific regions of the central nervous system.

Alternative waveforms have been extensively researched for SCS, the next development in DRG-S will probably be the introduction of burst technology. Burst stimulation, in contrast to tonic stimulation, delivers small packets of few pulses at regular intervals intending to mimic natural firing patterns in the nervous system. The spikes are non-linear and cause charge accumulation through temporal summation followed by passive discharge at the end of each burst. Burst stimulation has been shown to modulate the two ascending in the processing of pain: the medial pathway, involving the rostral to dorsal anterior

cingulate and anterior insular cortex and responsible for the unpleasantness of pain, and the lateral pathway, comprising the somatosensory cortex and processing the discriminatory component of pain. Tonic stimulation modulates only the lateral pathway and is therefore not associated with reductions in pain catastrophizing (Chakravarthy et al., 2019; De Ridder et al., 2021, 2015; Yearwood et al., 2020). Studies with burst stimulation have been performed for SCS in the dorsal columns, the effects of burst over the DRG are unknown but could dramatically increase the success of this therapy.

DRG-S and SCS might be integrated in the future for patients with pain in two different regions or even in a combined approach for a complex pain syndrome. Many patients with waning SCS benefit from DRG-S in a second step and need two different IPGs. Delivery of DRG-S with the IPG of an SCS is theoretically possible, but differences in stimulation parameters render is very inadequate. DRG-S needs much less energy than SCS, that steps at which stimulation amplitude can be increased in an IPG for SCS represent a too abrupt change for the DRG. The manufacturing of a combined IPG for both systems would benefit patients and increase the use of DRG-S, which can offer advantages over the revision of a previously implanted system for SCS.

The publication “Frequency dependency of therapeutic efficacy in dorsal root ganglion stimulation for neuropathic pain” stratified subjects by PainDETECT score and, even though no statistical significance could be achieved, reported that patients with predominant nociceptive component could benefit similarly from lower and higher stimulation frequencies (Piedade et al., 2022). This could be evidence that neuropathic and nociceptive pain components respond differently to stimulation. Much more than that, comprehension of the effect of stimulation over nociceptive pain could expand indications for DRG-S – and for neuromodulation as a whole – to a much broader pool of patients suffering from nociceptive pain, be it acute or chronic. Patients with acute back pain or herpes zoster, for instance, could benefit from temporary stimulation in the acute phase of pain, potentially avoiding the evolution to states of chronic neuropathic pain.

7.5 Conclusions

Dorsal root ganglion stimulation is a unique technique because it targets multiple sensitive fibers at the same time. The open lead placement technique, the stimulation in cervical and high-thoracic segments and as an add-on therapy to SCS amplify the access to DRG-S for patients with refractory chronic pain. The use of periradicular infiltration therapy may optimize the implantation algorithm, and the wise selection of stimulation frequency increases the efficacy of neuromodulation for these patients.

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9 Appendix

9.1 Open Microsurgical Dorsal Root Ganglion Lead Placement

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Open Microsurgical Dorsal Root Ganglion Lead Placement

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Introduction: Dorsal root ganglion stimulation (DRG) is a new but well-established neuromodulation technique allowing new indications and superiority to pre-existing stimulation techniques such as spinal cord stimulation in selected pain etiologies. Previous surgical procedures in the implantation area pose a challenge for the percutaneous technique and are therefore considered contraindications for DRG stimulation surgery. We describe the successful open DRG electrode placement in two patients with previous surgeries suffering from severe radiculopathy due to foraminal stenosis.

Methods: Percutaneous implantation attempts failed and an open laminotomy/foraminotomy followed by open lead placement was performed. Leads and loops were placed under the microscope, lead location was verified by x-ray during surgery. Leads and loops were kept in position with fibrin glue and fibrin sealant patches. No special tool was required for open lead placement.

Results: In both patients, surgery resulted in lead and loop placement resembling the results seen in percutaneous technique. Programming and stimulation results are similar to observations made following percutaneous techniques in one patient significantly lower stimulation amplitudes were necessary. In 18 and 12 months follow-up, respectively, lead location and paresthesia coverage were stable.

Conclusion: The option of open electrode placement should be taken into account following unsuccessful percutaneous lead placement. A combination of fibrin sealant patch and fibrin glue may be a good option for stabilization of the lead and specially of the strain relief loops in open placement. Knowledge of basic spinal surgery techniques and experience in percutaneous DRG stimulation is necessary to perform this procedure.

Keywords: Dorsal root ganglion stimulation, neuromodulation, neuropathic pain

Conflict of Interest: Philipp J. Slotty and Jan Vesper received travel expense reimbursement and speaker honoraria from St. Jude Medical/Abbott. Guilherme S. Piedade, Jan F. Cornelius, and Apostolos Chatzikalfas have no conflicts of interest.

INTRODUCTION

Dorsal root ganglion stimulation (DRG) is a new but well-established neuromodulation technique allowing new indications and superiority to pre-existing stimulation techniques such as spinal cord stimulation (SCS) in selected pain etiologies (1). With completion and publication of the ACCURATE study, DRG stimulation has become available in the United States (2). Due to the system´s reduced stiffness and susceptibility to damage compared to traditional SCS systems, DRG implantation technique is more constrained to normal anatomical situations. Previous surgical procedures in the implantation area are considered contraindications for DRG stimulation surgery. Despite this, successful DRG implantation with good outcome has been performed in our center with percutaneous implantation technique in patients with previous surgery, such as total disc replacement and spinal decompression procedures.

In two of our patients, we encountered anatomical changes due to previous surgeries, which despite multiple attempts and variations in approach rendered percutaneous lead implantation impossible. Both patients had received multidisciplinary pain treatment including neuropsychological assessment. No contraindications for neuromodulation were present. As we considered these patients ideal candidates for DRG regarding the anticipated therapeutic effect, we discussed the option of open lead placement. In both patients, an open microsurgical approach combining foraminotomy and visually controlled open lead placement resulted in a stable, radiographically correct, and therapeutically effective lead position. This article describes the basic approach and early outcome data. A video detailing the surgical technique is available online.

METHODS

Open DRG lead placement was performed in two patients so far. Both patients had previous spinal procedures, which were

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The findings in this manuscript have not been published previously. Parts of the findings in this article have been presented at the NANS meeting 2018.

Source of financial support: No external funding was used in this study.

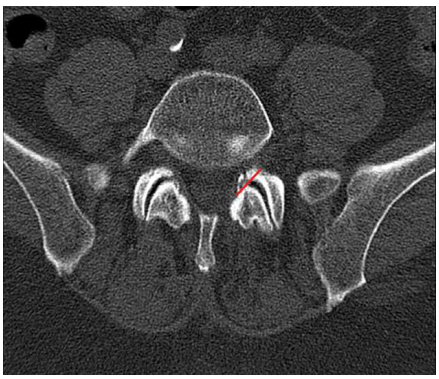

Figure 1. Preoperative CT of patient no. 1 showing the foraminal stenosis making the percutaneous approach impossible, the degree of foraminotomy performed is given by the right red line. [Color figure can be viewed at wileyonlinelibrary.com]

directly linked to the development of chronic neuropathic pain. Patient no. 1 had a long history of mainly L5 radicular pain before undergoing spinal decompression surgery with foraminal decompression of L5 and S1 on the left. Following an uneventful intraoperative course, the patient reported severe L5 pain immediately after surgery. Computed tomography (CT) imaging revealed an epidural bleeding compressing the L5 root and immediate revision surgery was performed. This left the patient with a severe neuropathic L5 pain. Conservative management did not result in sufficient pain reduction, periradicular infiltration of L5 reliably leaded to significant pain reduction for some weeks and 11 infiltrations were performed during the four years following surgery. A percutaneous DRG trial was performed in analgosedation aiming at the L5 and S1 roots on the left. Placement of the S1 lead posed no problem, but entry into the L5 foramen was not possible due to stenosis and the patient reported excruciating pain during the insertion. Therefore, surgery had to be stopped with only the S1 lead in place. Programming revealed that the area of pain could not

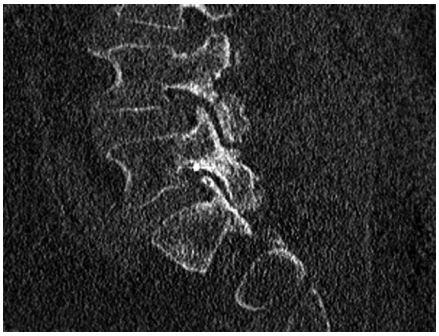

Figure 2. Placed lead in sagittal view in patient no. 1.

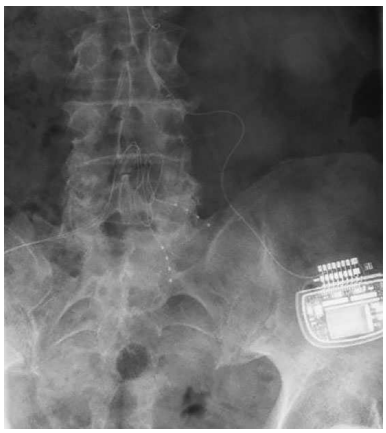

Figure 3. Postsurgical X-ray in patient no. 1 showing the strain relief loops, the extend of cranial epidural dissection performed (approximately one level) can be seen from the extend of loops reaching cranially.

be reached with the S1 electrode. We intensively discussed the situation with the patient and he consented to the attempt of an open lead placement. Surgery was performed in general anesthesia (GA) in a microsurgical manner. GA was chosen as the previous percutaneous procedure (especially while trying to enter the foramen) was very painful for the patient and the extent of dissection and foraminotomy necessary for lead placement was not clear for the team. The S1 electrode had to be removed for the foraminotomy of L5 (Fig. 1). Following foraminal decompression and cranial epidural dissection for loop placement, both electrodes could be placed under visual and radiographic control. The lead delivering sheath was not used as it proved to be too flexible to provide sufficient push into the foramen, it was brought in place with bayonet forceps. Following radiographic and electrophysiological control with motor stimulation, epidural strain relief loops were made and stabilized with fibrin sealant patch and fibrin glue. No additional anchoring was performed. The electrodes were tunneled to the IPG pocket and connected to a Proclaim DRG. Trialing with externalized leads was not performed as we expected programming to be more complex and take extended time compared to a percutaneous procedure. Wound closure was performed as in any spinal procedure.

Patient no. 2 is a 55-year-old female suffering from a severe complex regional pain syndrome in the left foot and lower leg following three spinal disc surgeries at L5/S1 and an S1 foraminal decompression. HF10 spinal cord stimulation did not result in significant pain relief. Similar to patient no. 1, percutaneous lead placement in S1 was successful and L5 was frustraneous due to foraminal stenosis. As S1 stimulation alone proved insufficient for pain control, an open approach was performed as described above, again resulting in a correct position of both leads.

Informed consent was obtained from the patients regarding analysis and publication of medical information and imaging. This study was approved by the local REB (internal no. 4077).

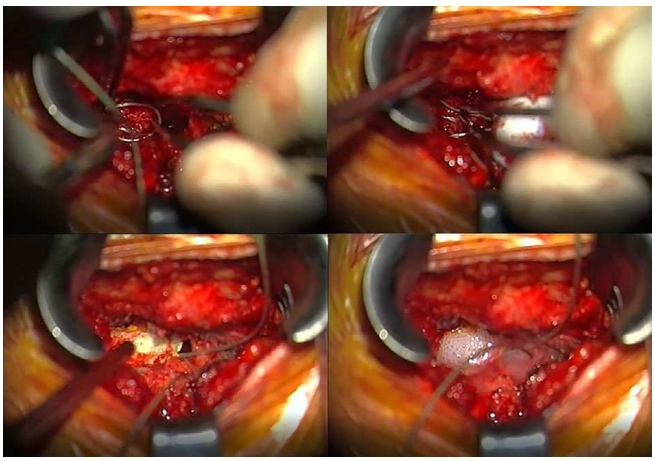

Figure 4. Panel of microscope photos taken during surgery, from top left to bottom right showing bayonet forceps used to push the electrode into the foramen without the sheath, construction of strain relief loops, stabilization of the situation with fibrin patch and fibrin glue. For more details, please see the video available with the manuscript. [Color figure can be viewed at wileyonlinelibrary.com]

RESULTS

In both cases, open DRG lead placement resulted in an electrophysiological and radiographic correct lead position. Surgery took about 90 min in both patients and was tolerated well with no adverse events (Figs. 2 and 3). These were the only cases in which this technique was used. Early postsurgical programming resulted in excellent coverage of the pain area and good pain reduction. Changes in paresthesia coverage and stimulation intensity are commonly observed in the early phase of DRG stimulation. We experienced a higher rate of changes in stimulation intensity and coverage in our two patients with open lead placement compared to patients following percutaneous lead placement and reprogramming had to be done at a higher frequency during this early course of treatment. Stable programming parameters were achieved at three month following surgery.

Following a period of excellent pain control during the first months of treatment (from VAS 9 to VAS 2), patient no. 1 reported a new increase in pain which could not be controlled with DRG stimulation alone. This increase is mainly triggered by increased activity and he required periradicular infiltrations but at a much lower frequency than prior to surgery. Tentative deactivation of the system leads to a significant increase in pain and pain medication is still significantly reduced.

Unfortunately, patient no. 2 did not receive reprogramming as required as she comes from a remote area. Reprogramming in our center was performed at 12 months follow-up and the patient reported good pain control for the first few weeks of treatment after which stimulation was not adjusted. She still reports a high variability of paresthesia coverage and stimulation intensity during movement. During reprogramming, an excellent coverage of the pain area could be achieved.

DISCUSSION

In numerous occasions, the option of open DRG lead placement has been discussed at national and international neuromodulation meetings. Two key questions were commonly discussed in these situations. First of all was how to stabilize the lead and especially the strain relief loops in open placement. This question is crucial as commonly the lead and loops are stabilized in the epidural layer between dura and posterior bone of the laminae. In an open approach, the lamina is reduced or completely removed, and stabilization of the loops has to be achieved in other ways. In our case, we choose a combination of fibrin sealant patch (Tachosil®) additionally stabilized by fibrin glue. The cranial portion of the loops was additionally placed in the cranial portion of the operating field in which the cranial lamina was intact (Fig. 4).

The second question that commonly arose in discussions was whether a special tool is required for open lead placement or if the percutaneous tool (sheath) can be used. In our experience, the sheath does not provide the required stiffness to allow open lead placement. Forward push of the electrode resulted in dorsal bending of the sheath. Following a couple of frustraneous maneuvers final lead placement was possible with a bayonet forceps. Dissection in the foramen had already been done during foraminotomy using ball-end hooks. Handling the lead with two forceps allowed precise maneuvering of the electrode to dorsally place of the electrode and create the strain relief loops.

Based on our first experience, we do not see the necessity to design a special tool for open DRG placement for two reasons: cases with previous surgery in the spinal area or even in the foramen itself that impede percutaneous lead placement are rare and analyzing the cases in which open DRG placement is necessary,

anatomical variations created by previous surgery are too variable to design a one-fits-all tool. For surgeons with sufficient experience in spinal surgery, required tools are already found in the neurosurgeons' armamentarium.

Both patients clearly suffered from neuropathic pain and foraminal decompression (which had to be performed for lead placement in both patients) alone was not sufficient for pain control. At 18 months follow-up, patient no. 1 clearly required DRG stimulation to sufficiently suppress his pain. In patient no. 2, the therapeutic efficacy could not be finally assessed due to the lack of reprogramming, paresthesia coverage indicates however an excellent and unchanged lead location at 12 months.

This article focuses on the surgical technique used for open DRG lead placement. The existence of differences in programming, long-term outcome or overall efficacy of DRG stimulation following an open approach should be determined in a larger group of patients. The technique described proved feasible for lead implantation without special tools and the technique of loop stabilization resulted in no dislocation at 12 and 18 months. However, as only two patients have been treated so far, conclusions have to be drawn very carefully.

CONCLUSION

Open DRG lead placement is possible, stable, and effective using a combination of the provided lead system and common spinal surgical techniques. A combination of fibrin sealant patch, cranial epidural dissection, and loop placement and fibrin glue can provide sufficient loop stability and thereby compensate for previous decompressive spinal surgery. Open DRG placement might be considered in promising cases in which the percutaneous implantation technique fails due to epidural scaring and foraminal stenosis.

Authorship Statements

Philipp J. Slotty conceived the idea; Jan F. Cornelius, Philipp J. Slotty, and Jan Vesper planned the procedure; Philipp J. Slotty and Jan F. Cornelius performed the procedure; Apostolos Chatzikalfas and Philipp J. Slotty made the follow-up; Philipp J. Slotty and Guilherme S. Piedade prepared the manuscript with input from all authors; all authors discussed the results and provided critical feedback.

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Neuromodulation 2018; E-pub ahead of print. DOI:10.1111/ner.12905

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

9.2 Cervical and High-Thoracic Dorsal Root Ganglion Stimulation in Chronic Neuropathic Pain

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Cervical and High-Thoracic Dorsal Root Ganglion Stimulation in Chronic Neuropathic Pain

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Introduction: Dorsal root ganglion stimulation is a meanwhile established but rather new technique of neuromodulation to treat chronic pain states of different origin. While being primarily used in the lumbar region, dorsal root ganglion (DRG) stimulation also can be used in the upper thoracic and cervical region with slight alterations of the surgical approach. This offers new therapeutic options especially in the treatment of neuropathic pain states of the upper extremities. Data on surgical technique, outcome and complications rates of DRG in this region are limited.

Materials and Methods: We report a consecutive series of 20 patients treated with DRG stimulation in the upper thoracic and cervical region. All patients suffered from chronic neuropathic pain unresponsive to best medical treatment. Main pain etiologies were trauma, spine surgery, postherpetic neuralgia, and peripheral nerve surgery. All patients were trialed with externalized electrodes prior to permanent pulse generator implantation. Routine clinical follow-up was performed during reprogramming sessions.

Results: Out of all 20 patients trialed, 18 were successfully trialed and implanted with a permanent stimulation system. The average pain relief after three months compared to the baseline was of 60.9% (mean VAS 8.5 to VAS 3.2). 77.8% of the patients reported a pain relief of at least 50% after three months. One patient developed a transient paresis of the arm caused by the procedure. She completely recovered within three months.

Conclusion: Cervical and upper thoracic DRG stimulation resulted in good overall response rates to trialing and similar pain relief when compared to DRG stimulation for groin and lower limb pain. A modified surgical approach has to be used when compared with lumbar DRG electrode placement. Surgery itself in this region is more complication prone and challenging.

Keywords: Dorsal root ganglion stimulation, neuromodulation, neuropathic pain

Conflict of Interest: Drs. Slotty and Vesper received travel expense reimbursement and speaker honoraria from Abbott. The remaining authors have no conflicts of interest to report. Parts of the findings in this article have been presented at the NANS 2017 meeting.

INTRODUCTION

The dorsal root ganglion (DRG) is one of the key structures in the development of neuropathic pain. It is a subdural structure, which contains the cell bodies of the primary sensory neurons. In neuropathic pain, lower potential threshold and subsequent spontaneous firing can be observed in the DRG cells (1). Low frequency stimulation can lower this abnormal activity by readjusting the potential threshold (2). In pathologies involving autonomic changes such as complex regional pain syndrome (CRPS), this readjustment even partially reverts autonomic changes by means not completely understood (3). DRG stimulation offers several advances more than traditional spinal cord stimulation on selected etiologies: Each DRG covers a selected dermatome and therefore allows more precisely targeted stimulation compared to spinal cord stimulation (SCS) with a stronger potential of pain suppression (4).

DRG stimulation received its CE mark in the European Union in 2011, later in 2015 the ACCURATE study proved the superiority of DRG stimulation in CRPS patients compared to conventional tonic SCS at 3 and 12 months follow-up (4,5). This landmark study led to FDA approval of DRG stimulation in the U.S. in February 2016. Indications are limited to chronic neuropathic pain associated with CRPS or peripheral causalgia, anatomical area for implantation is limited to sacral, lumbar, and the lower (T10 and below) thoracic nerve roots as well. In Europe, supranational approval does not include any anatomical limitations and the system is approved for treatment of chronic neuropathic pain regardless of origin.

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Many pathologies treated with DRG stimulation such as CRPS and chronic pain following peripheral nerve damage are not limited to the lower extremity. These diseases also can be found in the upper limbs and are therefore possibly promising targets for DRG stimulation. Additionally, certain conditions like intercostal neuralgia and postherpetic neuralgia (PHN) primarily exist in the thoracic region and therefore pose possible targets.

The particularities of DRG stimulation in the cervical and thoracic spine go beyond the surgical technique and involve programming, motor-stimulation thresholds, and variability of long-term stimulation efficacy. Although many studies were published on DRG stimulation for chronic pain in the lower extremities, little is known about the short- and long-term effects of this therapy for thoracic and upper limb pain. We report on a consecutive series of 20 cases of cervical and high-thoracic DRG stimulation.

MATERIALS AND METHODS

We report on a consecutive series of 20 patients treated with DRG stimulation (in 19 cases Axium™ System, Spinal Modulation, CA, USA; in one case Proclaim™ DRG Neurostimulation System, Abbott [formerly St. Jude Medical], IL, USA). All patients underwent DRG stimulation in the upper thoracic or cervical spine at the Department of Functional Neurosurgery and Stereotaxy of the Heinrich-Heine-University Düsseldorf between February 2013 and October 2016. Post-OP x-ray examples are given in Figures 1 and 2. All patients were aged 18 years or older and suffered from refractory chronic pain because of peripheral nerve or brachial plexus injuries, spinal cord surgery, PHN, CRPS II, or phantom limb pain. All patients were subject to multidisciplinary pain treatment prior to referral to our department. Electrode implantation was performed in general anesthesia in all patients, in most cases following a nerve root block to define the affected level. This was generally done in an outpatient setting under CT guidance. Electrode implantation technique differs from lumbar implantation: The needle position general has to be steeper in both the lateral and craniocaudal direction and especially in the cervical spine a same level approach is usually necessary. Maneuverability of the implantation system is generally very limited because of the thin CSF layer and the spinal cord. All patients were trialed with externalized electrodes (with extensions) for three to seven days; a successful trial was defined as at least 50% pain relief. Pain reduction was evaluated using the VAS scale. Patient data was prospectively collected and patient consent for data collection and publication was obtained prior to trialing. Follow-up data was collected during out-patient visits which were part of the clinical routine. This study was approved by the local REB (internal no. 4077).

RESULTS

Overall, 20 patients were assessed for cervical or high-thoracic DRG stimulation after having failed multidisciplinary best medical treatment for their condition. Mean age at time of implantation was 50.6 (SD 9.68) years (Table 1). Indications varied among CRPS (five cases), peripheral/plexus nerve injury (seven cases), PHN (two cases), postspine surgery pain (five cases), and phantom limb pain (one case). Of these patients, 90.0% (18/20) received a permanent neurostimulation system after having a successful trial period. In all patients, the implanted pulse generator (IPG) was implanted in the lower back, in most cases extensions were used in final implantation because of long route from electrode insertion point to the IPG. Patients with positive trial results had a mean overall perceived pain of 8.5 (SD 1.04) prior to implantation.

Six patients had one electrode implanted, nine received two electrodes and two patients a total of three. The overall pain perception at three months follow-up was 3.2 (SD 2.33) (n = 18), which calculates as an average pain relief after three months of 60.9%. Overall 77.8% of the patients had a positive short-term response. No early positive response was seen in three cases of peripheral nerve injury and in one PHN case. Early reduction in treatment effect requiring reprogramming was commonly observed during the first few months of treatment, a permanent loss of effect in the long-term refractory to reprogramming was found in one case of PHN and in one patient with postsurgical pain. The overall pain at six months follow-up was 3.9 (SD 2.25) (n = 13) and at 12 months 3.8 (SD 1.64) (n = 9).

In one patient, a transient paresis of the arm and hand was observed immediately following electrode implantation after an uneventful surgery. Immediate CT showed a regular electrode position with no epidural bleeding or significant stenosis caused by the implants. No signs of spinal cord injury were seen being aware that CT is limited in showing such alterations. The electrodes were left in place and the patient was successfully trialed. Permanent implantation was performed and the paresis completely resolved within three months. Two patients had their systems removed because of inefficacy. In three cases, revision-surgery of the leads and extensions was necessary because of dislocation or rupture. The small diameter and low mechanical resilience of the leads and extensions seem to pose a problem considering the long route down the IPG pocket, comparable to mechanical complications seen in occipital nerve stimulation surgery.

DISCUSSION

Similarly to the ACCURATE study, which evaluated DRG stimulation only for groin and lower limb pain and found 81.2% responsiveness at three months follow-up (3), 77.8% of the patients of our case series achieved a satisfactory short-term result. Our long-term success rates are unfortunately not representative because of a loss of follow-up. Huygen FJPM et al. published in 2015 a comparable case series of 19 patients with upper limb neuropathic pain treated with DRG stimulation, most of them with CRPS. A lower trial-to-permanent success rate was found (84.2%), the average pain relief at three months follow-up of 57.3% was similar to our results (6).

Although very similar, cervical and high-thoracic DRG stimulation has important particularities that make success and complication rates differ when compared to traditional stimulation for groin and lower limbs. Some pain etiologies are specific of the chest wall and upper limbs, such as intercostal neuralgia and PHN. Treating PHN is a major problem, it has challenged pain physicians and neurosurgeons for decades. The results we are observing with DRG stimulation so far are somewhat mixed (7–9). No comprehensive overview has been published so far and no common sense inside the neuromodulation society exists regarding recommendation for DRG stimulation in PHN. In our experience, stimulation of the affected ganglion itself does result in immediate and unbearable increase in pain under stimulation. Using the overlapping of dermatomes stimulation of adjacent segments does lead to a decrease in pain levels, especially regarding allodynia. This effect anyhow was only short termed in our

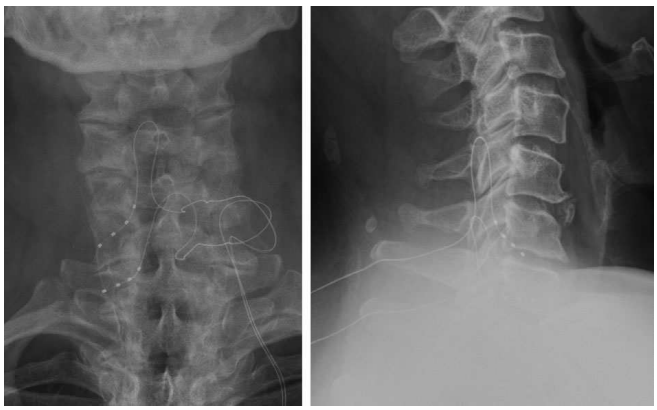

Figure 1. Early postsurgical lateral and a.p. x-ray of patient no. 10 with two DRG-electrodes in the C7 and C8 neuroforamen on the right side. Note the limited value of lateral x-ray in this region because of the shoulder girdle.

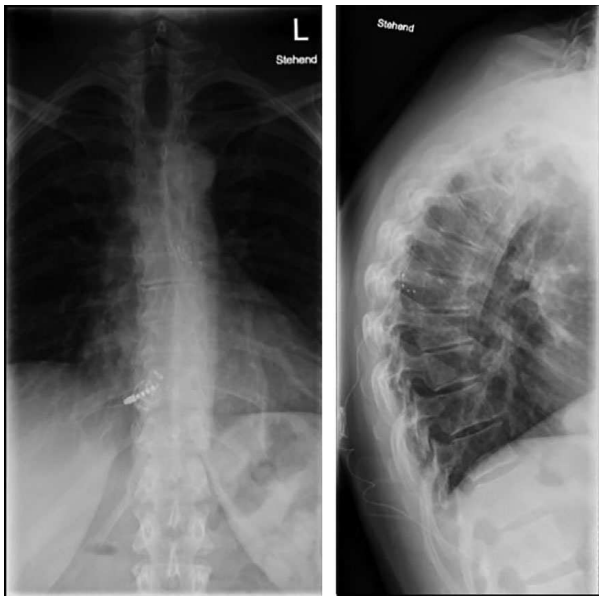

Figure 2. Thoracic lead placement in T7 in a rare case of DRG stimulation used for neuropathic pain on the left arm after the resection of a medullary hemangioblastoma. Lateral view confirms correct lead position. The patient achieved significant short- and long-term pain relief.

experience and could not be regained by intensive programming or stimulation holiday. We therefore would currently not generally recommend DRG stimulation in PHN, well aware that other experts in this field would disagree.

Some procedures restrict to upper limbs and thorax are classic causes of neuropathic pain that can be treated with neurostimulation. Nerve compression syndromes in the upper extremity such as ulnar and radial nerve compression are common and decompression surgery leaves a considerable number of patients with chronic pain syndromes and neuropathic pain (10). Cervical and upper thoracic DRG stimulation offers a valuable option in these patients and excellent results are seen in these patients.

Our case series includes one etiology in which DRG stimulation has to the best of our knowledge not been described for: Neuropathic pain following resection of spinal tumor at T2 to T3, in this case a medullary hemangioblastoma. The patient had

Table 1. Pain Development Following Successful Trials and Permanent Implants, Pain Changes Given in % Compared to Baseline.

No.	Age	Pain etiology	Underlying pathology	Lead location	VAS baseline	VAS @ 3 f/u	VAS @ 6 f/u	VAS @ 12 f/u
1	51	Resection of hemangioblastoma	Postsurgical pain	T7 left	8	2 (−75%)	4 (−50%)	3 (−62.5%)
2	68	Use of interferon for melanoma	Nerve injury	C8 left + right	10	2 (−80%)	2 (−80%)	2 (−80%)
3	55	Clavicle fracture	Nerve injury	C4 + C5 left	8	3 (−62.5%)	4 (−50%)	4 (−50%)
4	41	Arthroscopy	CRPS	C6 + C7 right	8	3 (−62.5%)	4 (−50%)	4 (−50%)
5	48	N. ulnaris decompression	CRPS	C8 left	9	1 (−88.9%)	2 (−77.8%)	2 (−77.8%)
6	52	Trauma	Nerve injury	C6 right	8	6 (−25%)	6 (−25%)	5 (−37.5%)
7	44	Disc herniation	Postsurgical pain	T1 + T2 right	9	3 (−66.7%)	4 (−55.6%)	6 (−33.3%)
8	61	Herpes zoster	Postherpetic neuralgia	C8, T1, T2 right	8	3 (−62.5%)	6 (−37.5%)	6 (−37.5%)
9	51	Resection of arachnoid cyst	Postsurgical pain	T5 + T9 left	9	1 (−88.9%)	1 (−88.9%)	2 (−77.8%)
10	46	Radiotherapy for breast cancer	CRPS	C7 + C8 right	10	0 (−100%)	0 (−100%)	n/a
11	40	Clavicle fracture	Nerve injury	C4 + C5 right	7	6 (−14.3%)	6 (−14.3%)	n/a
12	41	Resection of neuroma	CRPS	C6 + C7 right	10	3 (−70%)	4 (−60%)	n/a
13	53	Carpal tunel release	Nerve injury	C7 right	8	8 (0%)	8 (0%)	Explantation
14	51	Abscess drainage in axilla	CRPS	T1 + T2 right	7	2 (−71.4%)	n/a	n/a
15	45	Disc herniation	Postsurgical pain	C6 left	8	0 (−100%)	n/a	n/a
16	38	Arm amputation	Phantom pain	C7 + T1 left	10	5 (−50%)	n/a	n/a
17	51	Spinal stenosis	Postsurgical pain	C8 left + right	9	2 (−77.8%)	n/a	n/a
18	75	Herpes zoster	Postherpetic neuralgia	T4, T5, T7 left	7	7 (0%)	Explantation	n/a

radiating pain to the left arm, which led to the diagnosis of a medullary tumor. Following resection of the tumor in another hospital, the pain did not subside and became chronic. She presented with constant scapular pain and exertional radiation to the left arm and to the ventral chest wall. A significant short- and long-term pain relief was achieved after the placement of a lead in T7 left. Going into an anatomical region with DRG electrodes in which complex medullary surgery had been performed crosses the border of what we currently think our stimulation hardware is suitable for and which indications can be covered by DRG stimulation.

DRG stimulation of cervical and high-thoracic spinal ganglia deserves special technical considerations. Because of anatomic differences, needle placement should take a steeper approach through the interlaminar space to reach the target neuroforamen. The presence of the spinal cord (as opposed to the cauda equine in the lumbar region), the thin CSF layer and the unavoidable steeper approach lead to an increased risk of spinal cord lesion. A too lateral needle entry point intending to reduce dorsal pressure on the spinal cord will likely increase the risk of a ventral electrode position, leading to motor stimulation. Lead dislocations are likely more frequent in cervical DRG stimulation because of the high and frequent mobility of the spine in this region. In almost all cases, extensions were used because of trialing with permanent electrodes and due the long route from electrode to IPG pocket. As in occipital nerve stimulation, subcutaneous strain-relief loops turned out to be useful, but extensions fracture requiring revisions surgery were observed. In these cases, the insulation of the extension was intact, whereas the wire inside was torn. This was visible on x-ray in all cases. With this complications observed, surgery for the extensions and IPG might have to be reevaluated. A pectoral IPG pocket might offer a good alternative.

CONCLUSIONS

Cervical and upper thoracic DRG stimulation is feasible and results in good overall response rates to trialing and excellent long-term pain relief in primary responders. A modified surgical approach has to be used when compared with lumbar DRG electrode placement. Surgery itself in this region is more complication prone and challenging. Implanters should be in depth familiar with lumbar DRG implantation technique and spinal surgery in the thoracic and cervical region.

Authorship Statements

Dr. Slotty conceived the idea for the manuscript. Drs. Vesper, Slotty and Chatzikalfas performed the procedures and follow-ups. Dr. Piedade developed the project. Drs. Piedade and Slotty wrote the manuscript with input from all authors. All authors approved the final version of the manuscript.

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9.3 Synergetic efficacy of simultaneous DRG- and traditional spinal cord stimulation

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ORIGINAL ARTICLE - FUNCTIONAL NEUROSURGERY - PAIN

Synergetic efficacy of simultaneous DRG- and traditional spinal cord stimulation

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Abstract
Background Dorsal root ganglion stimulation has established its role in chronic pain states and is commonly used as an alternative treatment to traditional spinal cord stimulation. Due to its approach, DRG stimulation is preferably used in pain conditions affecting a small area or a distinct nerve root. In selected patients, a combination of both techniques might be useful.
Methods We report a series of five patients with chronic pain treated with DRG stimulation and traditional spinal cord stimulation from 2011 to 2018. Pain was reported on the VAS scale at the baseline, before and 12 months after the second procedure.
Results All patients suffered from back and lower limb pain, four with a FBSS syndrome, one with CRPS. In all but one patient, SCS was implanted first and complemented with a DRG in the course (4–90 months between procedures). An additional stimulation system was implanted because the previous stimulation failed to reach the pain area or because the patient had an altered perception of other pain component after stimulation. All but one patient had a consistent and satisfying therapeutic effect with both systems activated.
Conclusion The combination of dorsal root ganglion and traditional spinal cord stimulation is surgically and technically feasible. In selected patients, the combination of both methods offers an option to alleviate pain states not sufficiently or not efficiently treated with one method alone. The introduction of IPGs combining SCS and DRG stimulation paradigms might be useful to increase acceptance of this option.

Keywords Dorsal root ganglion stimulation · Spinal cord stimulation · Neuropathic pain · Neuromodulation

Introduction

Dorsal root ganglion (DRG) stimulation achieved general acknowledgment after the results of the ACCURATE study, which showed superiority of the new therapy when compared to the conventional tonic spinal cord stimulation (SCS) in the treatment of complex regional pain syndrome (CRPS) of the lower limbs [1]. DRG stimulation, now approved by the FDA, was established as an independent treatment modality that has since then been preferred for focal chronic pain, with normally distinctive nerve roots affected. The fact that DRG stimulation allows more precise targeting of stimulation and likely a higher degree of pain relief made it also a valuable resource for certain patients already under spinal cord stimulation that achieved insufficient results.

Most of the failures of spinal cord stimulation occur in spite of sufficient paresthesia on the target area, as reported by Jang et al., and this is particularly more frequent in the case of postherpetic neuralgia, spinal cord lesions and in patients with allodynia dominant pain [2]. In the remaining 34% of the reported failures, reprogramming and lead revision are effective to solve loss of treatment efficacy, but some complex patients remain with insufficient stimulation results. Not only anatomic variations or the variability of SCS lead positions may play a role, but patients may first become aware of a different, more focal pain component when the general back pain is partially treated or the other way around. For the cases

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of complex chronic pain that overcome the therapeutic possibilities of spinal cord stimulation alone, DRG stimulation may complement results and even provide a more efficient stimulation pattern. Little is known about the feasibility and the efficacy of this combined approach.

Methods

We report a series of five patients treated with dorsal root ganglion stimulation and spinal cord stimulation at the Department of Functional Neurosurgery and Stereotaxy. The first procedure was performed in February 2011, the last one in June 2018. In the five cases, pain was restricted to the back and lower limbs and was refractory to multidisciplinary pain treatment. Prior to SCS system implantation, all patients were trialed and reported at least 50% pain relief. Before implantation of a DRG stimulation system, a CT-guided selective nerve root block confirmed the affected level [5]. Pain reduction was evaluated using the VAS scale, the first baseline consisting of pain level in the 4 weeks preceding the first procedure. The second baseline considered both the pain treated with the first procedure and the new or insufficiently treated preexisting pain component. The pain reported 12 months following the second procedure combining the efficacy of both stimulation methods was also assessed. Data from patients with simultaneous SCS und DRG stimulation were selected from data collected in a larger prospective study with DRG stimulation conducted in our Department (IRB approval no. 4077).

Results

A total of five patients with simultaneous SCS and DRG stimulation were included. In the same period, for a matter of comparison, there were 117 implantations of a DRG stimulation system and 913 of an SCS system at the same Department. Four patients had a primary spinal disease that needed a surgical treatment and developed a failed back surgery syndrome (FBSS); etiologies included spinal fracture, disc herniation and spinal stenosis. In one case, a chronic regional pain syndrome type II emerged after an ankle fracture. The average age when the first procedure was performed was 54.8 years; most of the patients were male (4/5). SCS was the first procedure of choice in four cases and without exception led to a significant pain relief. Patient 3 was the only one to be primarily treated with DRG stimulation because of his pain character mainly localized in the groin, which could also be adequately treated with a single electrode in L2. The time until a second procedure varied between 4 and 90 months and was in average 32.2 months (Table 1).

In the first two cases and in patient 5, the SCS was even after extensive reprogramming not technically able to reach distant pain areas, leaving a significant focal pain area untreated. Patients 3 and 4, however, reported another much more relevant pain after the first procedure in areas not covered by stimulation. Patient 3 was unsatisfied with a back pain that he first noticed after adequate treatment of his groin pain with DRG stimulation (Figs. 1 and 2); patient 4 perceived a significant increase in his known sciatica after alleviation in his CRPS with SCS as the first procedure.

All patients except number 4 had a significant pain relief after the second procedure. Patients 1, 2 and 5 had an adequate coverage of the residual pain after SCS; the localized residual painful area could be appropriately targeted with DRG stimulation following a previous test with nerve root block. The newly perceived lumbago of patient 3 could be addressed with an SCS, used only this time as a second procedure. The patient 4, with a CRPS, reported continuous relief of his original pain with an SCS, but DRG stimulation from L4 to S1 afterwards was not capable of significantly changing the old sciatica despite adequate coverage.

Programming had to be performed for each device individually with the other device switched off, allowing the patients to distinguish between paraesthesia induced by each stimulation method. No technical difficulties or interferences were observed during programming or with the systems running. In all patients, both systems were activated. For the surgical

Table 1 Pain development following both neurostimulation procedures

Patient	Age	Etiology	Pathology	First procedure	Interval (month)	Second procedure	VAS baseline 1	VAS baseline 2	VAS at 12 f/u
1	62	Spinal fracture	FBSS	SCS Th9-10	4	DRG L1-2	9	3 (− 67%), 7	3 (− 57%)
2	52	Disc herniation	FBSS	SCS Th6-7	90	DRG S1	9	4 (− 56%), 8	3 (− 63%)
3	64	Spinal stenosis	FBSS	DRG L2	5	SCS Th10-12	9	2 (− 78%), 8	2 (− 75%)
4	43	Ankle fracture	CRPS	SCS Th7-11	11	DRG L4-S1	10	5 (− 50%), 8	7 (− 13%)
5	53	Spinal stenosis	FBSS	SCS Th8-10	51	DRG S1	8	3 (− 63%), 10	5 (− 50%)

The age at the time of the first procedure was presented. Interval between the procedures was indicated in months and pain intensity in the VAS scale. The first baseline indicates pain intensity in the 4 weeks preceding the first procedure, the second baseline considers both the pain treated with the first procedure (with percentual change) and the new or insufficiently treated pain component prior to the second procedure. Pain intensity of this second painful component is reported in a 12-month follow-up

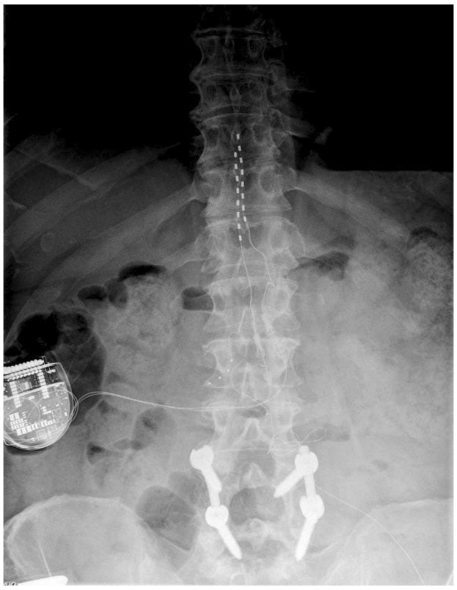

Fig. 1 X-ray of patient 3 suffering from groin pain on the right following a herniotomie and a severe FBSS with mainly leg pain

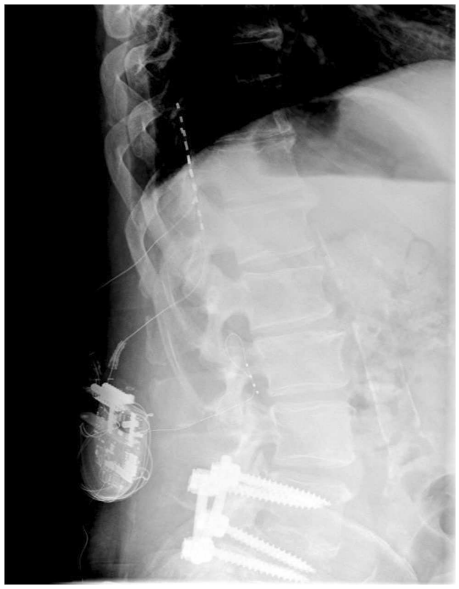

Fig. 2 Lateral x-ray of the same patient 3, note the DRG lead running cranial and dorsal in the foramen

planning, detailed analysis of the already implanted components was performed mainly based on x-ray and, in some cases on cat scans. No surgical complications were encountered. Except in patient 2, which had a Specify® SCS system produced by Medtronic, all other neurostimulation systems implanted in this study were offered by Abbott-Progidy® in three cases and Eon Mini in one case for SCS®, Proclaim® in three patients and Axium® in the remaining two for DRG stimulation. In all patients, both IPGs were implanted dorsally.

Discussion

The need of a second functional procedure could be explained by a failure of the first procedure to completely cover the preoperative pain, which is a very superficial and intuitive answer that, however, hardly relates to the complexity of most patients submitted to multiple neuromodulation techniques. Cases 1, 2 and 4 indeed illustrate how DRG stimulation can appropriately address the more focal pain left untreated by an SCS with a huge stimulation area even after extensive reprogramming. Even with all currently available complex stimulation paradigms as burst, high density, high frequency, microdosing and so on, traditional SCS is limited by the rather large area of effect, which might result in overstimulation in some areas and insufficient (under-) stimulation in others [1]. Some patients, normally the most complex and chronically compromised ones, are affected by various, different pain components and their perception of them can be changed when the most intense pain component is treated. Patient 3 did not even perceive his back pain before his groin pain was successfully addressed by DRG stimulation.

Dorsal root ganglion stimulation and spinal cord stimulation used together have interesting clinical results and pose little additional technical and surgical challenges. As the spinal segments responsible for the lower limbs are significantly higher than their correspondent lumbar dorsal root ganglia, the risk of lead dislocation during a second procedure is low. This might differ significantly in other areas of the spine. Especially in the cervical spine, anatomical targets to treat FBSS of the neck and upper extremity pain are very close to each other and combining SCS and DRG in this area is likely surgically more challenging. We do not have experience with a combination therapy in this area yet, despite our large series of cervical and high-thoracic DRG stimulation [4]. As in any other operative system revision, the risk of damage to the already implanted system in a second operation is always present but was not observed in the patients reported.

DRG stimulation and SCS complement each other for the case of remaining pain area, and to achieve optimal results, the

dedicated neuromodulist should be deeply familiar with both stimulation methods. Although insufficient pain relief remains as the major problem, unrequired paresthesia is also an issue of concern for patients with a stimulation area that is much larger than necessary to treat a more limited pain. SCS has comprehensively a high proportion of unrequired paresthesia, reaching 210% of the patients' total painful body surface area in a study conducted by Deer et al. Even burst and similar designs provoke paraesthesia with high amplitude. The combination with DRG stimulation, which reaches an unrequired paresthesia of only 20% of the painful area in the same study [1], could bring more comfort to patients. In this setting, integration of stimulation devices could avoid the shortcomings of two simultaneous and separate stimulation systems.

Implantable pulse generators (IPG) currently available in the market were developed either for SCS or for DRG stimulation. Patients benefiting from both treatments have the inconvenience of carrying two IPGs, which normally need to be replaced separately too. The development of hybrid IPGs, for both SCS and DRG stimulation, is feasible with the current technology and could reduce the total number of surgical procedures in the lifetime of an integrated stimulation system. There are already commercially available IPGs that use a similar principle and layer different waveforms simultaneously and therefore enable a combination therapy [3], but the system is currently restricted to SCS. An IPG compatible with both therapies should be able to deliver waves with high amplitude for SCS, enough to stimulate the spinal cord across the dura mater, and low amplitude for DRG stimulation, because in this last case, the electrodes are surrounded by cerebrospinal fluid.

Conclusion

The combination of dorsal root ganglion and traditional spinal cord stimulation is surgically and technically feasible. In selected patients, the combination of both methods offers an option to alleviate pain states not sufficiently or not efficiently treated with one method alone. This introduction of IPGs combining SCS and DRG stimulation paradigms might increase acceptance of this option.

Authors' contributions PJS and GSP conceived the idea, JV, PJS and GSP performed the procedures and follow-ups, GSP and PJS developed the project, GSP and PJS wrote the manuscript with input from all authors. All authors approved the final version of the manuscript.

Parts of the findings in this paper have been presented at the INS 14th World Congress.

Compliance with ethical standards

Conflict of interest PJS and JV received travel expense reimbursement and speaker honoraria from Abbott. All authors certify that they have no financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee of the Medical School of the Heinrich-Heine-Universität Düsseldorf and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

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9.4 The role of periradicular infiltration in dorsal root ganglion stimulation for chronic neuropathic pain

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The role of periradicular infiltration in dorsal root ganglion stimulation for chronic neuropathic pain

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Abstract

Background Targeting the correct spinal level is essential in dorsal root ganglion (DRG) stimulation. Anatomical selection of the DRG alone is not ideal since the pain area is not necessarily confined to the borders of the dermatomes. This study aims to establish the role of periradicular infiltration therapy (PRT) in the preoperative assessment of the correct level for DRG stimulation performed under general anesthesia.

Method We report a prospective study of 20 patients selected for DRG stimulation and submitted to a PRT for identification of the spinal level. Lead implantation for the stimulation trial occurred under general anesthesia: 19 patients experienced positive results and underwent implantation of the pulse generator. All patients suffered from chronic neuropathic pain unresponsive to best medical treatment. PRT levels were compared with the levels targeted with DRG leads. Patients were followed for up to 12 months; pain intensity and coverage of the painful area were assessed.

Results In 12 patients, the trial leads were placed on the same level as previously tested positive by PRT. In 6 patients, leads were placed in the PRT target and additionally in adjacent spinal levels. In one case, the selected target for the trial diverged from the PRT target because of intense fibrosis in the chosen level. Coverage of the target area of at least 50% was achieved by two-thirds of the patients. For the six subjects with additional implanted leads as a consequence of the PRT results, 80% achieved a coverage of at least 50%. A total of 47.4% of the patients achieved sustained significant pain relief in the last follow-up. None of the patients needed a repeated surgery for implantation of additional leads.

Conclusions PRT is a helpful tool to confirm the stimulation targets. A PRT preceding the stimulation trial is an additional opportunity to optimize the coverage of the target area with stimulation-induced paresthesia for patients operated under general anesthesia.

Keywords Periradicular infiltration · Dorsal root ganglion Stimulation · Neuromodulation · Chronic pain

Introduction

The therapy of chronic neuropathic pain remains a challenge today. To date, only 30 to 40% of patients with neuropathic pain can be treated satisfactorily with medication alone [3]. Conventional spinal cord stimulation (SCS) has been used successfully since 1967 to treat neuropathic pain. Yet, the results are not completely satisfying in all patient populations. The dorsal root ganglion (DRG) offers a relatively new target for neuromodulation due to its important role in the development and maintenance of chronic pain, as well as its anatomically convenient accessibility. DRG stimulation represents an effective supplement to SCS by providing precise, targeted stimulation even of discrete pain regions in areas that are difficult to reach with conventional SCS and improved patient outcomes for certain pain disorders [5]. The ACCURATE study has shown that DRG stimulation provides long-term, sustained pain relief for specific pain disorders and painful regions, being superior to conventional tonic SCS in 3 and 12-month studies [2]. Targeting the correct spinal level is

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essential for a successful pain treatment. Moreover, the number of electrodes is limited to 4 by the contacts of the implantable pulse generator and, each additional electrode increases the risk of surgical complications, such as infection or dislocation.

The initial selection of the correct DRG for stimulation is mostly based on the pain distribution among dermatomes. After a spinal level is targeted, a DRG stimulation lead is normally implanted with an extension lead externalized for a stimulation trial. If the patient benefits from this trial, the implantable pulse generator (IPG) can be inserted in a second procedure. Alternatively, both leads and IPG can be implanted in the same procedure, all-in-one. The issue is that an anatomical selection of the DRG alone is not ideal since the pain area is not necessarily confined to the borders of the dermatomes. Additionally, dermatomes often show unique distributions with overlap.

In the literature, selective radiofrequency (RF) stimulation of the DRG has been discussed as a method for predicting the correct spinal level for stimulation, possibly giving important information for lead implantation in a stimulation trial or even in an all-in-one procedure [4]. Only two case studies on RF stimulation prior to DRG stimulation have been published so far; no standard preoperative procedure for DRG stimulation has been established yet. As a result, most surgeons have their own approach to solve the problem of pre-surgical targeting. A frequently used alternative is a CT-guided periradicular infiltration therapy (PRT). This procedure uses local anesthetics and can be easily performed on the preoperative day, efficiently helping the surgeon to choose the spinal level for DRG stimulation. There are no valid data associating PRT results with DRG outcomes so far. This study aims to establish the role of PRT in a preoperative assessment of the correct level for DRG stimulation regarding the coverage of the painful area with stimulation-induced paresthesia.

Methods

This is a prospective single-arm study that evaluates the outcomes of patients undergoing implantation of a DRG stimulation system. Twenty patients scheduled for DRG stimulation were prospectively observed between 2016 and 2018. All patients were at least 18 years old with an indication for DRG stimulation due to a chronic pain disorder refractory to best pharmacological treatment. No patients were excluded due to previously known intolerances to local anesthetics administered as part of PRT or to other contraindications to the procedure.

The baseline pain assessment was performed using a visual analog scale (VAS). On the same day or in the following days a PRT of the presumptive affected DRG was performed [6], the target level was chosen on a clinical basis and in some cases multiple levels were chosen because the clinical examination by the responsible surgeon showed that the pain extended over several dermatomes. In our institution, a diagnostic PRT consists of the injection of bupivacaine 2.5 mg/mL. In cervical roots, 2 mL is the maximal injected volume, while in lumbar roots generally 3 mL is used. Dexamethasone is injected with bupivacaine only in therapeutic PRTs and was therefore not used. Bupivacaine has an elimination half-life of 143 min following epidural administration [1] and the PRT is performed at least 24 h before lead implantation. Patients were clinically evaluated by the responsible surgeon up to 2 h after the PRT, sensibility to light touch was assessed with either a tissue or cotton. During the consultation, the patient was asked about pain relief and to what extent the painful area was covered by the PRT (completely, partially, not at all). PRT testing was considered positive if patients responded with pain relief in the corresponding painful area. Complete pain relief was not required for a positive PRT assessment, as the goal was to find the appropriate level of stimulation and not to achieve complete pain relief with PRT. If the anesthetized region and the pain region were not congruent, another PRT of a different, usually adjacent spinal level was performed usually 1 day after the first one at the discretion of the responsible surgeon. After congruent PRT results to the painful area, lead placement was performed for trial stimulation or exceptionally in an all-in-one procedure. At the discretion of the surgeon, additional leads were implanted in adjacent levels if there was insufficient coverage of the pain region with the PRT effect. Negative PRT results were not considered exclusion criteria for a DRG trial.

For the trial period, one to three leads were placed using a minimally invasive epidural approach under general anesthesia. No intraoperative paresthesia testing was done. Leads were anchored to the muscular fascia and were attached to an external trial stimulator using externalized extensions; stimulation was provided for 3 to 7 days. At the end of the trial, a new evaluation of the pain condition was performed using VAS. With a pain reduction of 50% and/or objective functional improvement of the patient, the trial was considered successful and the implantation of the IPG was performed (Proclaim DRG; Abbott Neurological, St. Jude Medical, Minneapolis, MN, USA). Patients with an increased surgical risk as well as patients with a clearly positive PRT result according to the experience of the responsible surgeon underwent all-in-one surgery. After the implantation of the complete neurostimulation system, the patient was interviewed in the regular out-patient visits within 1 week, as well as 1, 3, 6, and 12 months postoperatively using VAS, questionnaires, and pain/paresthesia maps. The existence of paraesthesia in the previously painful area as well as the percentage of painful area covered with paraesthesia was documented. Patients with a pain relief of at least 50% under DRG stimulation were considered responsive.

All study elements were approved by the local ethics committee, and each patient gave written informed consent prior to the beginning of any study activities.

Results

Twenty patients with the indication for DRG stimulation were evaluated regarding pain development (Fig. 1). Preoperative PRT was performed in all patients; no complications were observed. When results were not clear or incongruent with the painful area, a second PRT was performed, and it was the case of 4 patients; for a congruent result, at least one PRT should be congruent. Overall, five patients were affected by CRPS, four patients by FBSS, and most patients had another form of postsurgical neuropathic pain. Mean age was 54.8 years in the group; mean follow-up time was 10.9 months.

From overall 20 included patients, PRT was congruent with the pain region in 18 cases (90%). The two patients with incongruent results were however trialed for DRG because the pain region was clearly related to a very specific dermatome—one case did not achieve relevant pain relief during the trial and was later treated with an SCS; the other one was responsive during the trial and progressed to IPG implantation (patient 14). Because this single patient underwent an SCS, DRG stimulation was performed on 19 patients during this study.

In the 18 patients with congruent PRT, five patients were selected for an all-in-one implantation at the discretion of the treating surgeon because the PRT yielded an adequate coverage of the painful area with a significant pain reduction. Out of this group, only two patients (40%) reported relevant sustained pain relief under DRG stimulation.

The remaining 13 patients with congruent PRT that were not considered for an all-in-one implantation were submitted to a trial; 12 patients had a positive trial. These subjects had a sustained significant pain relief under DRG stimulation in 53.8% of the cases in the last follow-up (7/13). The only congruent PRT result but insufficient trial result was selected for the implantation of the IPG at discretion of the treating neurosurgeon for reasons that include significant functional improvement. No significant pain relief was achieved in this particular case. Considering now all patient groups, mean reduction in pain intensity under DRG stimulation was 31.7%; a total of 47.4% of the patients achieved sustained significant pain relief in the last follow-up (9/19).

In 11 patients, the trial leads were placed on the same level as previously tested positive by PRT (Table 1). In 6 patients, leads were placed in the PRT target and additionally in adjacent spinal levels, meaning that the PRT modified the original plan. In 15 patients, the leads were implanted on the same level as previously tested in the trial; in 2 patients, additional leads were implanted as a consequence of the trial results (patients 8 and 10) (Fig. 2). In the particular case of patient 13, the implantation of a DRG lead in S1 was technically not possible because of fibrosis, and the patient had a lead in L5 implanted.

Data to coverage of the painful area with paraesthesia was available for 12 patients, all of them with a previous congruent PRT result. Two-thirds of them reported a coverage of the target area of at least 50%. For the six patients with additional implanted leads as a consequence of the PRT results (patients 2, 5, 6, 8, 9, and 10), 80% achieved a coverage of at least 50%, with data being unavailable for patient 8.

A total of 7 patients underwent revision surgery, which included broken leads and lead defects, among other causes. One patient died before the end of the study unrelated to the DRG system or surgery, the remaining 18 implanted patients were observed over a period of 12 months.

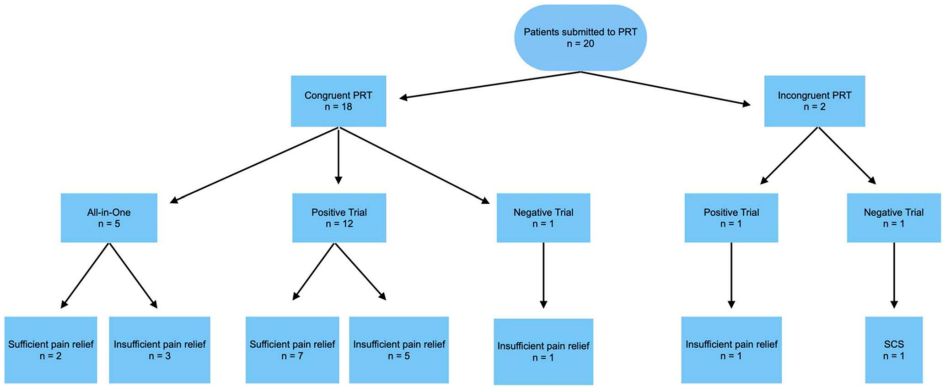

Fig. 1 Flow diagram of included subjects

Table 1 PRT and DRG levels, clinical outcomes

	Sex	Age	Diagnosis	PRT level	PRT congruence	DRG level	VAS Baseline	VAS 1 mo	VAS 3 mo	VAS 6 mo	VAS 12 mo	Coverage
1	M	58	FBSS	S1 left	+	S1 left	9	5	10	10	9 (0%)	30%
2	F	41	Pain after peripheral nerve injury	C6, C7 right	+	C6, C7 right	10	-	7	5 (−50%)		100%
3	F	27	FBSS	S1 left	+	S1 left	8	-	0	0	0 (−100%)	100%
4	F	52	CRPS I	C6 right	+	C6 right	7	5	7	6	7 (0%)	90%
5	F	29	CRPS II	L5 left	+	L5, S1 left	6	1	-	2	3 (−50%)	20%
6	M	56	Postarthroplasty	L3, L4 right	+	L2, L3, L4 right	5	5	7	4	2 (−60%)	100%
7	M	64	FBSS	L2 right	+	L2 right	7	7	7	1	3 (−57%)	-
8	M	44	CRPS II	L4 left	+	L4, L5, S1 left	10	-	9	10	9 (−10%)	-
9	M	42	CRPS II	L5 right	+	L5, S1 right	8	6	-	8	8 (0%)	50%
10	F	35	Postthoracotomy	Th11 right	+	Th9, Th10, Th11 right	8	5	5	3	2 (−75%)	100%
11	F	77	Postarthroplasty	L3, L4 right	+	L3, L4 right	8	9	8	4	3 (−63%)	-
12	M	68	Postarthroplasty	L3 right	+	L3, L4 right	3	2	6	-	6 (+50%)	0%
13	M	45	FBSS	S1 left	+	L5 left	9	-	-	-	7 (−22%)	-
14	M	80	Postarthroplasty	L3, L4 right	−	L3, L4 right	8	5	6	7	8 (0%)	-
15	F	51	Postsalpingectomy	Th12, L1 left	+	Th12, L1 left	9	7	9	-	9 (0%)	0%
16	M	69	Postarthroplasty	L3, L4 right	+	L3, L4 right	7	2	2	3	6 (−14%)	100%
17	M	82	Postarthroplasty	L2, L3 left	+	L2, L3 left	8	6	4	4	7 (−13%)	100%
18	F	49	Posttraumatic	S2 both	+	S2 both	9	0	1 (−89%)	-	-	-
19	M	79	Postherniotomy	L1, L2 right	+	L1, L2 right	10	0	0	5 (−50%)	-	-
20	F	49	CRPS I	Th9, Th12 right	−	None	8	-	-	-	-	-

A second PRT was done in patients 1 (S1 left), 2 (C6 right), 10 (Th11 right), and 17 (L2 and L3 left). All-in-one procedures were the case of patients 5, 11, 12, 16, and 17. Implantation of a DRG lead in S1 was technically not possible in patient 13 due to fibrosis. *PRT* periradicular therapy, *DRG* dorsal root ganglion, *VAS* visual analog scale, *FBSS* failed back surgery syndrome, *CRPS* complex regional pain syndrome

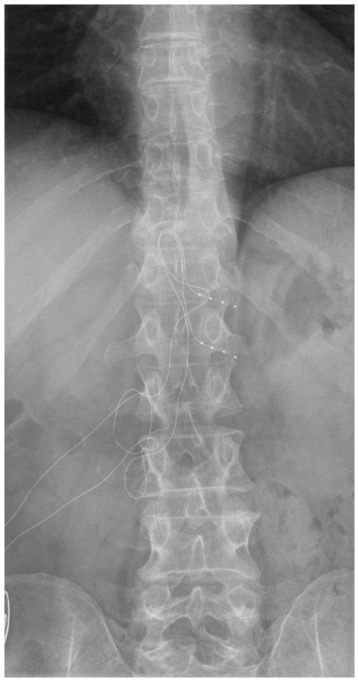

Fig. 2 DRG leads implanted in Th12 and L1 on the left side, the patient suffered from chronic pain after a salpingectomy

Discussion

The aim of the study was to investigate whether the preoperative periradicular therapy is eligible in a preoperative protocol for identifying the correct spinal level for DRG stimulation regarding the coverage of the painful area with stimulation-induced paresthesia. Compared to the past case studies on methods for predicting targets for DRG stimulation by Zuidema et al. [7] on retrograde transforaminal paresthesia mapping, with 3 patients with groin pain, and by Hunter et al. on radiofrequency stimulation, with 4 patients with post-amputation pain of the lower extremity [4], a considerably larger number of patients could be examined. Similarly, the selection of patients investigated in this study was not limited to an underlying disease or localization of pain. The study thus provides a good representative picture of the patient population of neuropathic pain. In comparison to the mentioned studies, the present study enabled an analysis of a longer-term stimulation result after successful PRT testing.

In our department, PRT has become the standard of care in almost all patients being screened for DRG for confirmation of the target level. Bupivacaine is usually preferred and has a longer elimination half-life than lidocaine. Lead implantation occurs on the following day so that no analgesic effect of the PRT should be present. In this study, however, all lead implantations were done under general anesthesia without paresthesia control. Even when the initial PRT does not cover the entire painful area, it orientates the surgeon when choosing the target DRG. If the first PRT result is not congruent with the painful area, a second PRT may be helpful, which was the case of three patients in this study. In case of insufficient coverage after PRT, the direct implantation of another leads in the trial without prior testing becomes more justifiable when a first PRT confirmed at least partial improvement. As a single-arm study, no comparisons can be made with the coverage rates of a control group that did not undergo a preoperative PRT. Our study was, however, able to show that the PRT results modified the original targets established by the responsible surgeons based on anatomical landmarks in a considerable number of patients. It is true that insufficient coverage can also be detected in the trial phase, but the preoperative PRT turns the trial into a second opportunity to evaluate the adequate coverage of the painful area before implantation of the definitive system. Unfortunately, we did not find any references regarding the incidence of second or even third procedures for the implantation of new DRG leads after the implantation of the IPG because of insufficient pain coverage. It is intuitive, however, that a preoperative PRT could reduce the length of hospital stay and the risks of new surgical procedures because more affected levels are earlier identified additionally to the clinically inferred ones. It might offer an additional option to reconsider the neuromodulation strategy for every individual patient. In this study with 19 subjects submitted to DRG stimulation, a second operation for implantation of new leads did not occur.

Not as intuitive is the possible predictive value of preoperative PRT over the outcomes of DRG stimulation. These therapies have different mechanisms of action, but such a relationship would be of considerable interest, as it might indicate which patients would not benefit from DRG stimulation—whose technique for lead placement is particularly more difficult when compared with traditional spinal cord stimulation. For a matter of comparison, the positive predictive value of a successful trial for sustained significant pain relief achieved 53.8% in this study. As only one patient had a negative trial and was submitted to DRG stimulation later, nothing can be said about its negative predictive value based on these data.

Particularly interesting is the case of the five patients submitted to an all-in-one implantation of DRG leads following a very successful PRT testing. In these cases, when PRT results were most promising considering adequate coverage and reduction of pain intensity, the positive predictive value for final significant pain relief was only 40% and 50% for coverage of at least 50% of the painful area. This result regarding pain

reduction is lower than the predictive value of a trial (53.8%), which remains as the gold standard for the selection of patients for implantation of the definitive system. The predictive value regarding coverage of the painful area was also lower than the value obtained considering all 12 patients with available coverage data (67%). The indication for an all-in-one implantation of DRG leads is given at discretion of the responsible surgeon and should be specially considered in patients with higher surgical risk, but data of this study with a limited sample size supports a stepwise approach with a stimulation trial—independent of how promising PRT results are.

Limitations

This study evaluated only the congruence of PRT effect with the painful area and not the effect of PRT over the pain intensity. No conclusions can be drawn regarding its predictive value to stimulation outcomes. It is however relevant to mention that the variability of PRT results is influenced by physician experience and technical aspects, such as anesthetics used and addition of steroids. Therefore, insufficient pain relief after PRT would not change our indication for a DRG trial, as it was the case with patient 14. The inclusion of PRT in our clinical routine is independent of its positive predictive value over final clinical outcomes.

Conclusion

The success of the DRG stimulation depends on the correct lead placement, and PRT is a helpful tool to confirm the stimulation targets. A PRT preceding the stimulation trial represents an additional opportunity to optimize the coverage of the target area with stimulation-induced paresthesia for patients operated under general anesthesia.

Author contribution JV and PJS conceived the idea, GSP, JV, and PJS performed the procedures and follow-ups, HS developed the project, HS and GSP wrote the manuscript with input from all authors. All authors approved the final version of the manuscript.

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Declarations

Ethics approval All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest PJS and JV received travel expense reimbursement and speaker honoraria from Abbott, JV is paid consultant of Abbott.

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9.5 Frequency dependency of therapeutic efficacy in dorsal root ganglion stimulation for neuropathic pain

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ORIGINAL ARTICLE - FUNCTIONAL NEUROSURGERY - PAIN

Frequency dependency of therapeutic efficacy in dorsal root ganglion stimulation for neuropathic pain

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Abstract

Background The influence of the stimulation frequency on the outcomes of dorsal root ganglion stimulation (DRG-S) to treat pain is not well understood. It is assumed that specific neural components dedicated to different tasks in the DRG can be preferably influenced at specific frequencies. The identification of frequencies designed for the type of pain and the ratio of neuropathic versus nociceptive pain might improve overall pain control and open new indications in DRG-S.

Method We report on a randomized double-blind clinical trial with a crossover design. Patients with a permanent DRG-S system underwent phases of stimulation with 20 Hz, 40 Hz, 60 Hz, 80 Hz, and sham in a randomized order. Each phase lasted for 4 days and was followed by a 2-day washout period. Pain intensity and quality of life were assessed with visual analog scale (VAS), McGill Pain Questionnaire (MPQ), EQ-5D, and Beck Depression Inventory (BDI). Analgesics intake was assessed.

Results Overall 19 patients were included in the study. CRPS was the most frequent pain etiology (7). Five patients had a PainDetect score of 12 or lower at baseline. The mean VAS before the system was implanted was 8.6 and 3.9 at the baseline. Pain intensity was reduced to 3.7 by the stimulation with 20 Hz but increased with higher frequencies reaching 5.8 at 80 Hz. A significant difference among the groups was shown over all variables examined (VAS, MPQ, EQ-5D, BDI). The best results were seen at 20 Hz for all variables, including the smallest increase in pain medication consumption.

Conclusions The choice of the stimulation frequency shows a clear influence on pain reduction and quality of life. Lower stimulation frequencies seem to be most effective in neuropathic pain. Further studies are required to determine whether specific frequencies should be preferred based on the condition treated.

Keywords Neuropathic pain · Dorsal root ganglion stimulation · Frequency

Abbreviations

DRG-S	Dorsal root ganglion stimulation
VAS	Visual analog scale
MPQ	McGill Pain Questionnaire
EQ-5D	EuroQol-5D
BDI	Beck Depression Inventory
CRPS	Complex regional pain syndrome
DRG	Dorsal root ganglion
DRKS	German Register of Clinical Studies
IPG	Implantable pulse generator
SD	Standard deviation

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Introduction

Dorsal root ganglion (DRG) stimulation has been effectively used in the treatment of neuropathic pain of different etiologies. In neuropathic pain, spontaneous firing as a consequence of lower action potential thresholds can be observed in the DRG neurons [12]. Different stimulation frequencies could lower this abnormal activity with different intensities by readjusting the action potential threshold. In a traditional view of "stimulation dose," patients requiring more pain relief would respond to a higher total electrical energy delivery, which is dependent on current, pulse width, and

stimulation frequency [11]. However, recent studies have shown that DRG-S with lower frequencies—and therefore with lower total energy delivery—could be an effective alternative. A sub-analysis of the ACCURATE study [3] reported paresthesia-free subjects using DRG-S that achieved similar pain relief with lower amplitudes and frequencies [10]. Koetsier et al. were able to show a delayed washout effect of DRG-S in the treatment of painful diabetic neuropathy in rats [8]. Chapman et al. reported a case series with tapering of stimulation frequencies in twenty patients with refractory back pain down to 4 Hz and reported sustained pain relief [2].

It is assumed that specific neural components of the DRG can be influenced in a targeted manner by the selection of different frequencies and that different pain patterns can be optimally treated with different frequencies. Little is known about the effect of stimulation frequency over the clinical outcomes of DRG-S. We report on the first randomized double-blind clinical trial testing mid-frequency DRG-S in patients with neuropathic pain.

Materials and methods

Patients aged above 18 years old with a DRG stimulation system implanted and followed-up at the Department of Neurosurgery of the Heinrich-Heine-University Düsseldorf were invited to participate in the study. Written informed consent was obtained. Individuals were excluded from the trial in case of further significant pain that might confound the study assessments. Nineteen patients participated in the study. The study was approved by the Ethics Committee of the Medical Faculty under the number 2020–1120 and was registered at the German Clinical Trials Register (DRKS) under DRKS00022557.

Patients were evaluated for neuropathic pain with PainDetect (0–38 points) at the baseline. All patients tested five different stimulation parameter settings in a randomized order: stimulation frequencies of 20 Hz, 40 Hz, 60 Hz, 80 Hz, and sham stimulation. Sham means amplitude set at 0.025 mA, the minimum amplitude allowed, so that the IPG indicates to the patient stimulation on, but delivers only ineffective stimulation. Patients were programmed at subthreshold for each tested frequency; amplitude was corrected in each case. Patients and investigators were blinded, and a study nurse had access to unblinded data. Each stimulation parameter setting was tested for 4 days and was followed by a 2-day washout period. The stimulation parameters were programmed in advance by a study nurse and were randomly changed by the patients each week at home. The stimulation amplitude was programmed to subthreshold levels individually for each frequency. At the end of each phase, the patients were interviewed by phone and completed numbered questionnaires.

At baseline, VAS and clinical parameters were assessed, and pre DRG-S pain data was collected from charts. During the study, patients underwent assessment of pain intensity and quality using the visual analog scale and McGill Pain Questionnaire (MPQ, 0–78 points), of quality of life using EQ-5D (Index 0–1), and of the prevalence of depression using the Beck Depression Inventory (BDI, 0–63 points). Any additional intake of analgesics was documented by the patients.

Statistical analysis

Patients' demographics were analyzed using descriptive statistics and presented as frequency and percentage for categorical variables, and as numbers, means, minima, maxima, and standard deviations (SD) for continuous variables. Statistical analysis was performed using SPSS 19 software (IBM Cooperation, USA) and GraphPad Prism 8.0.2.

Repeated measurement one-way ANOVA was used for comparison between baseline data and measurements at the different frequency settings applying Tukey's multiple comparison test. An alpha error of 0.05 was considered significant, and 0.01 was considered highly significant.

Results

A total number of 19 patients participated in the study. The mean age was 53 years (range: 25–80) and the patients were using DRG-S for a mean of 17.2 months (range: 4–102). The most common pain etiology was chronic regional pain syndrome (CRPS) (7 subjects), followed by postsurgical pain after implantation of joint prosthesis (4), postherpetic neuralgia (3), nerve injury after resection of neurinomas (2), traumatic nerve injury (2), and diabetic polyneuropathy (1). Fourteen patients had a PainDetect Score of 12 or higher (76.7%), indicating higher probability of neuropathic pain. Patients reported a mean VAS of 8.6 (SD 1.0) before the implantation of the DRG-S system and a mean baseline VAS of 3.9 (SD 1.9). All patients had already been programmed in the clinical routine and had reached a stable therapeutic response. All patients had a stimulation frequency of 20 Hz at study start.

Even at subthreshold level with corrected amplitude, some patients experienced at higher frequencies a change in the paresthesia field. Amplitude was reduced in these cases. No patient had painful paresthesia nor motor stimulation.

Results for mean VAS for 20 Hz, 40 Hz, 60 Hz, 80 Hz, and sham stimulation were 3.7 (SD 1.9), 4.9 (SD 2.2), 5.8 (SD 1.9), 5.8 (SD 1.9), and 8.6 (SD 1.3) respectively (Table 1). 20 Hz achieved significantly lower pain intensity

Table 1 Pain intensity under stimulation frequencies of 20 Hz, 40 Hz, 60 Hz, 80 Hz, and sham stimulation. *CRPS*, complex regional pain syndrome; *SD*, standard deviation

No	Age	Pain etiology	PainDetect	VAS pre DRG-S	VAS baseline	VAS 20 Hz	VAS 40 Hz	VAS 60 Hz	VAS 80 Hz	VAS Sham
1	26	Postherpetic neuralgia	17	8	4	4	8	6	4	8
2	59	CRPS	9	9	7	5	7	7	7	8
3	59	Postsurgical after implantation of joint prothesis	19	10	5	4	4	5	6	10
4	38	Nerve injury after neuroma resection	12	8	3	2	3	2	2	8
5	60	Postsurgical after implantation of joint prothesis	19	8	2	2	3	4	4	7
6	53	Postherpetic neuralgia	5	8	0	0	2	4	4	6
7	35	CRPS	24	9	3	3	1	9	7	9
8	70	Postherpetic neuralgia	19	8	1	2	5	8	8	8
9	65	Postsurgical after implantation of joint prothesis	14	8	5	5	7	8	8	9
10	80	CRPS	9	8	3	3	3	4	5	7
11	71	Traumatic nerve injury	9	8	3	3	4	5	5	7
12	40	CRPS	32	10	6	7	8	8	8	10
13	56	CRPS	13	8	4	3	7	7	9	9
14	35	CRPS	34	10	5	4	7	7	5	10
15	74	Diabetic polyneuropathy	15	6	4	3	4	5	4	10
16	48	Postsurgical after herniotomy	12	9	7	7	7	5	5	8
17	25	CRPS	20	9	7	7	7	6	8	9
18	50	Nerve injury after neuroma resection	16	10	4	5	4	8	7	10
19	55	Postsurgical after implantation of joint prothesis	7	9	2	2	3	4	4	10
		Mean (SD)	16 (7.9)	8.57 (1.01)	3.94 (1.98)	3.73 (1.91)	4.94 (2.19)	5.89 (1.88)	5.78 (1.93)	8.57 (1.26)

than 40 Hz ($p = 0.004$) and any other tested stimulation parameters ($p < 0.001$). 40 Hz did not result in significantly better results than 60 Hz ($p = 0.086$), nor did 60 Hz have lower pain intensities than 80 Hz ($p = 0.695$) (Fig. 1). Although the overall trend and statistics favor lower stimulation frequencies, two patients preferred higher stimulation frequencies and reported better pain control. In both cases, amplitude remained at the necessary level for subthreshold stimulation.

The same trend was seen with the McGill Pain Questionnaire, which resulted in 30.8 (SD 15.8), 33.1 (SD 17.3), 35.9 (SD 16.9), 36.3 (SD 14.2), and 46.5 (SD 17.2) points. In this case, statistical significance was only achieved when comparing MPQ results of 20 Hz and 80 Hz ($p = 0.047$). When analyzing quality of life, EQ-5D indexes were 0.76 (SD 0.16), 0.69 (SD 0.26), 0.59 (SD 0.30), 0.58 (SD 0.30), and 0.24 (SD 0.37). The index for 20 Hz was not significantly higher than for 40 Hz ($p = 0.071$), but than for 60 Hz and 80 Hz ($p = 0.001$).

Beck Depression Inventory resulted for the same groups 9.9 (SD 7.8), 10.8 (SD 7.1), 11.9 (SD 8.9), 13.6 (SD 8.7), and 15.5 (SD 10.2) points. Under 20 Hz, BDI was not significantly lower than under 40 Hz ($p = 0.19$), but under 60 Hz ($p = 0.033$) and 80 Hz ($p = 0.005$). Table 2 shows comprehensive data with the mean difference and statistical significance.

Although only assessed in a very basic fashion (increase in medication yes/no), the lowest number of patients reported an increased need for analgesic medication during 20 Hz stimulation (9 subjects), and 13 patients referred increased analgesics intake during 40 Hz stimulation and 16 subjects under 60 Hz and 80 Hz, whereas all 19 patients reported an increase during sham stimulation.

When stratified by PainDetect, a higher overall VAS and a higher mean difference in the VAS between stimulation frequencies were observed in the patients with a score > 12 without reaching statistical significance. The overall observation regarding better pain control with lower frequencies was still observed.

Discussion

Dorsal root ganglion stimulation is an effective form of treatment for chronic, especially neuropathic, pain conditions. The choice of stimulation frequency shows a clear influence on pain reduction and the associated quality of life. Lower stimulation frequencies seem to be most effective in the examined pain etiologies, which is explained by the pathophysiology of pain processing.

A possible mechanism of action of DRG-S involves the activation of low-threshold mechanoreceptors, which are Aß-, Aδ-, and C-fiber afferents transmitting fine touch sensation. These fibers play an important role also inhibiting painful stimuli at the level of the dorsal horn [5]. Animal studies in vitro showed that high- and low-frequency DRG

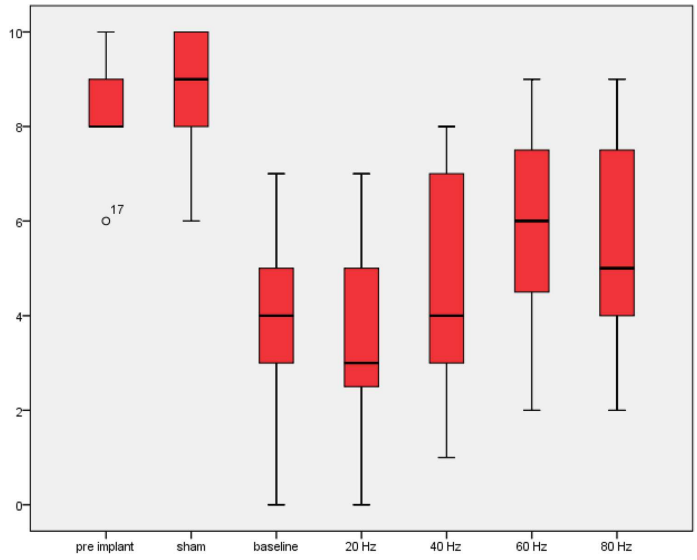

Fig. 1 Mean VAS pre DRG-S, under sham stimulation, at baseline and under 20, 40, 60, and 80 Hz

Table 2 Mean difference between baseline data and treatment groups adjusted with Tukey's multiple comparison. No EQ5D, BDI, and MGPQ data is available at baseline and only VAS data is available pre DRG-S implantation. *Significant (<0.05); **Highly significant (<0.01). n.s., not significant

		pre DRG-S	Baseline	20 Hz	40 Hz	60 Hz	80 Hz	Sham
pre DRG-S	VAS		4.632 (**)	4.842 (**)	3.632 (**)	2.684 (**)	2.789 (**)	0.000 (n.s.)
	MGPQ							
	EQ5D							
	BDI							
Baseline	VAS	4.632 (**)		0.210 (n.s.)	− 1.000 (n.s.)	− 1.947 (*)	− 1.842 (*)	− 4.632 (**)
	MGPQ							
	EQ5D							
	BDI							
20 Hz	VAS	4.842 (**)	0,210 (n.s.)		− 1.211 (*)	− 2.158 (**)	− 2.053 (**)	− 4.842 (**)
	MGPQ				− 2.263 (n.s.)	− 5.053 (n.s.)	− 5.474 (*)	− 15.68 (*)
	EQ5D				0.07495 (n.s.)	0.1702 (*)	0.1733 (*)	0.5187 (*)
	BDI				− 0.8947 (n.s.)	− 2.053 (n.s.)	− 3.684 (*)	− 5579 (**)
40 Hz	VAS	3.632 (**)	− 1.000 (n.s.)	− 1.211 (*)		− 0.9474 (n.s.)	− 0.8421 (n.s.)	− 3.632 (**)
	MGPQ			− 2.263 (n.s.)		− 2.789 (n.s.)	− 3.211 (n.s.)	− 13.42 (*)
	EQ5D			0.07495 (n.s.)		0.09526 (n.s.)	0.09837 (n.s.)	0.4438 (*)
	BDI			− 0.8947 (n.s.)		− 1.158 (n.s.)	− 2.789 (n.s.)	− 4.684 (*)
60 Hz	VAS	2.684 (**)	− 1.947 (*)	− 2.158 (**)	− 0.9474 (n.s.)		0.1053 (n.s.)	− 2.684 (**)
	MGPQ			− 5.053 (n.s.)	− 2.789 (n.s.)		− 0.4211 (n.s.)	− 10.63 (*)
	EQ5D			0.1702 (*)	0.09526 (n.s.)		0.0031 (n.s.)	0.3485 (*)
	BDI			− 2.053 (n.s.)	− 1.158 (n.s.)		− 1.632 (n.s.)	− 3.526 (n.s.)
80 Hz	VAS	2.789 (**)	− 1.842 (*)	− 2.053 (**)	− 0.8421 (n.s.)	0.1053 (n.s.)		− 2.789 (**)
	MGPQ			− 5.474 (*)	− 3.211 (n.s.)	-0.4211 (n.s.)		− 10.21 (*)
	EQ5D			0.1733 (*)	0.09837 (n.s.)	0.0031 (n.s.)		0.3454 (*)
	BDI			− 3.684 (*)	− 2.789 (n.s.)	− 1.632 (n.s.)		− 1.895 (n.s.)
sham	VAS	0.000 (n.s.)	− 4.632 (**)	− 4.842 (**)	− 3.632 (**)	− 2.684 (**)	− 2.789 (**)	
	MGPQ			− 15.68 (*)	− 13.42 (*)	− 10.63 (*)	− 10.21 (*)	
	EQ5D			0.5187 (*)	0.4438 (*)	0.3485 (*)	0.3454 (*)	
	BDI			− 5579 (**)	− 4.684 (*)	− 3.526 (n.s.)	− 1.895 (n.s.)	

stimulations act over different inhibitory pathways in rats. Whereas low-frequency stimulation of 0.2–1.0 Hz promoted a pain relief that was suspended with naloxone, the effect of high-frequency stimulation of 100 Hz was reversed with GABA and glycine antagonists in transverse slices of rat spinal cords [6, 7, 13]. The different roles of high- and low-frequency DRG stimulations have not been investigated in humans so far.

The reason why low- and high-frequency stimulations may work differently is probably the phase locking of low-threshold mechanoreceptors. This occurs when neurons fire at the same frequency as the stimulation and it is only possible at certain stimulation frequencies depending on neurophysiological properties of each fiber. As shown by Arcourt et al. in a study with optogenetically modified rats, low-threshold mechanoreceptors in these animals were subject to phase locking for frequencies up to 20 Hz, after which neurons start asynchronous firing [1]. Assuming similar properties in the human population, for which such physiological studies lack, phase locking could be an explanation for the findings of the present study—the first of its type, to the best of our knowledge, with most patients reporting higher pain intensities under higher stimulation frequencies.

The frequency effect was less evident in patients with a PainDetect score under 12, which indicates a less pronounced neuropathic component in the overall pain. Dichotomizing the group by the PainDetect score did not result in a statistically significant difference but in a trend. This study might simply be underpowered to clearly reveal this difference. These subjects with an important nociceptive pain, which did also benefit from DRG-S in this trial like patients with classic neuropathic pain, seem not to rely exclusively on the endogenous intraspinal opioid

inhibitory pathway for pain relief. This interesting finding is yet to be confirmed with further studies and could help extending neuromodulation for the much larger population with nociceptive pain.

In our study, we used a 2-day washout period. In most patients, DRG-S elicits fast to immediate response regarding pain control, but some effects of DRG-S go beyond pain control, e.g., autonomic symptoms in CRPS. These commonly take longer to become effective and are therefore likely underestimated in this study. For studies investigating only pain control, the washout period could even be shortened. In studies investigating autonomic effects, the stimulation interval and washout periods should be extended. This is especially important in studies looking into the efficacy of neuromodulation to modulate the function of immune system, e.g., to treat CRPS, osteoarthritis, and similar disorders [4].

This trial is the first to investigate the influence of stimulation frequencies in DRG-S in a double-blind, randomized, prospective setting. We tested frequencies down to 20 Hz—a mid-frequency stimulation. We recognize the potential of even lower stimulation frequencies down to 4 Hz, as shown by Chapman in his important case series [2]. We are currently further investigating the influence of stimulation frequency in DRG-S with the aim to predict optimal stimulation frequencies based in the underlying condition and the proportion of neuropathic and nociceptive pain. The relevance of such studies goes far beyond the expected elongation of battery lifetime; the focus is the targeted approach of different nerve fibers with unique neurophysiological properties. Additionally, stimulation with lower intensities and less energy-transfer is thought to induce less habituation preventing loss of effect over time [9].

Limitations

The study results are limited by the fact that all the subjects were using 20 Hz of stimulation frequency for a long time prior to the beginning of the study.

Conclusions

The choice of the stimulation frequency shows a clear influence on the pain reduction and the associated well-being and quality of life of the patient. Lower stimulation frequencies seem to be most effective for neuropathic pain. As soon as larger similar studies are available, conclusions will be drawn regarding the functioning of the DRG in different pain etiologies and the pathophysiology of pain processing.

Author contribution GSP and PJS conceived the idea; SG, GSP, JV, PJS, and PSMP performed the procedures and follow-ups; SB and PSMP developed the project; GSP wrote the manuscript with input from all authors. All authors approved the final version of the manuscript.

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Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was required.

Conflict of interest PJS and JV received travel expense reimbursement and speaker honoraria from Abbott. JV is paid consultant of Abbott. GSP certifies that he has no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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