Non-Randomized Study

Effectiveness of "Transgrade" Epidural Technique for Dorsal Root Ganglion Stimulation. A Retrospective, Single-Center, Case Series for Chronic Focal Neuropathic Pain

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Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 03-05-2019 Revised manuscript received: 04-03-2019 Accepted for publication: 06-11-2019

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Background: The recent interest in targeting the dorsal root ganglion (DRG) has led to the development of new techniques of electrode placement. In this article, we describe a new "Transgrade" approach to the DRG, accessing the contralateral interlaminar space and steering the lead out the opposite foramen.

Objectives: The purpose of this study was to evaluate the Transgrade technique to the DRG in the management of focal neuropathic pain, predominately complex regional pain syndrome in terms of efficacy and safety.

Study Design: A retrospective, observational review of all patients selected for DRG stimulation using the Transgrade technique to the DRG.

Setting: Pain Management and Neuromodulation Centre, Guys and St. Thomas NHS Foundation Trust, London, United Kingdom.

Methods: Data were taken from a hospital password-protected database. All patients were contacted by telephone for Numeric Rating Scale (NRS-11) score, Patient Global Impression of Change (PGIC) score, and complications. A patient responder was defined as having a PGIC score of 6 or 7, and a 2-point reduction from baseline NRS-11.

Results: A total of 39 patients (46% women) with a mean age of 46 years (± 2) underwent a trial of DRG stimulation that resulted in an implantation rate of 82% (32 of 39). The responder rates, according to NRS-11 and PGIC results, were 87% (28 of 32) at 6 weeks and 66% (21 of 32) at a mean of 18 months (± 1.8) follow-up. Pocket pain was the most common complication, occurring in 7 of 32 (22%) patients, and the lead migration rate was 3 out of 57 leads placed (5.2%). A burst protocol was the favored method of stimulation in the majority of patients, 25 of 32 (78%).

Limitations: Retrospective nature of design, small sample size.

Conclusions: The Transgrade technique of placing DRG leads offers an alternative method that is safe and effective. New methods of stimulation to the DRG offer more choice and potentially better efficacy for patients with chronic neuropathic pain.

Key words: Neuromodulation, dorsal root ganglion, neuropathic pain, complex regional pain syndrome, spinal cord stimulation, chronic pain, implantable neurostimulators, spinal nerve root stimulation

Pain Physician 2019: 22:601-611

Commentary on this manuscript found on Page 613

Neurostimulation has been available for the treatment of neuropathic pain for more than 50 years (1-4). The initial and still the most common stimulation target is the dorsal column of the spinal cord (4,5). Dorsal column stimulation, often referred to as spinal cord stimulation (SCS), has most often used perceptible paresthesia to target areas of chronic pain (3,6). Although this approach can provide significant relief for a group of patients, there often can be undesirable paresthesia in areas that are not painful to the patient (7-10). An example of this would be leg stimulation when there is only low back pain, or leg stimulation when there is only ankle pain. In addition, certain areas, such as the pelvis and feet, have been relatively difficult to consistently stimulate with an SCS approach.

Our understanding of nerve injury from preclinical models have illustrated maladaptive, pathological reorganization of the dorsal root ganglion (DRG) (11-17). There is evidence to suggest the DRG is an active participant in the development and maintenance of neuropathic pain (11,18,19). Targeted neurostimulation of the DRG has emerged as an important therapeutic option (20-34). Deer et al. (34) performed an initial case series demonstrating the clinical feasibility of DRG stimulation in different neuropathic pain conditions. DRG stimulation was initially reserved for cases refractory to conventional dorsal column stimulation, cases in which the patient experienced untoward stimulation with changes in posture, and in which dorsal column lead placement was unable to capture the affected painful area (30-32). However, recent studies have demonstrated strong evidence for DRG stimulation as a first-line treatment in many cases, most notably complex regional pain syndrome (CRPS) (28). DRG stimulation has also enabled us to treat other chronic pain conditions more effectively, which include testicular pain (35), peripheral neuropathy (36,37), knee pain, groin pain, and pelvic pain (26,38).

DRG stimulation offers a novel technique of stimulation in comparison to SCS, potentially with a different mechanistic action (11,39). Anatomic benefits include direct stimulation of the nerve cell body, and less use of power due to proximity of the target in the neuroforamina. DRG stimulation also allows us to target the first major site of physiologic modulation prior to entry into the dorsal horn. Some of the proposed theories of DRG stimulation effect include preferential hyperexcitability of A-delta fibers from anatomic sites of pain, improved inhibition of maladaptive C-fiber firing, modulation of immune cells and glia, down-regulation of abnormal ion channels, and a reversal of maladaptive genetic changes (11). However, we currently lack physiologic evidence to state that we are successfully stimulating the DRG without other structures (e.g., peripheral and central nerves). Radiologic confirmation of the DRG with electrode proximity has yet to be determined.

There have been several approaches to the DRG that have been championed, including an intraspinal approach that directs the stimulator lead from the epidural space out the nerve root, and a transforaminal approach that accesses the DRG "from the outside to the inside" (24). A retrograde approach has also been used for many years for nerve root and sacral nerve stimulation (40-42). The "Transgrade" approach of entry into the epidural space places a lead in the neuroforamina from the opposite side of the interlaminar space, which may have operational and long-term benefits.

At present, there are few available implantable devices for DRG stimulation available in Europe and the United States. The Abbott system (Proclaim DRG; Abbott Neurological, St. Jude Medical, Plano, TX) is comprised of 4 electrodes of 1.25-mm width spaced 5 mm apart, which uses bipolar stimulation between these electrodes and has a contact range of 20 mm in total. This system uses a symmetric biphasic, conventional tonic method of stimulation. A wireless device from Stimwave (Stimwave Inc., Pompano Beach, FL) is also available.

The Boston Scientific Neuromodulation (Valencia, CA) SCS device is able to provide monopolar stimulation by placing an anode at the implantable pulse generator (IPG) and cathode at the electrode site, allowing for a potentially smaller, more focused monopolar circumferential field of stimulation. The lead consists of 8 electrode contacts, each 3 mm in length, spaced 1 mm apart, comprising 31 mm in total. This system offers novel waveforms aside from tonic stimulation and includes a burst protocol. Currently, there has not been a publication of a case series on the use of this device for DRG stimulation.

To our knowledge, we present the first case series using a tightly spaced contact octapolar lead to effect a different technique for epidural delivery for DRG stimulation in patients with chronic neuropathic pain of various etiologies, to demonstrate feasibility of the technique.

Methods

Description of Technique

Patients were selected for DRG stimulation by a multidisciplinary team based on a diagnosis of chronic neuropathic pain recalcitrant to conventional medical therapies. All patients underwent a multidisciplinary neuromodulation pain management assessment comprised of psychological and physical functioning prior to the trial. The level of pathology was identified using physical examination, conventional neurodiagnostic testing, and DRG mapping (43).

Transgrade DRG Lead Placement

Position

Patients were positioned prone with a pillow under the abdomen to reduce lumbar lordosis. The appropriate spinal levels were identified by fluoroscopy and marked with a surgical marker. The entry point was also marked over the contralateral superior articular process of the corresponding vertebra, or more caudal to this point depending on the level. Generally, entry at levels L4-S1 require a slightly greater caudal angle of approach (Fig. 1).

Needle and Lead Insertion

A paramedian incision is made over the intended point of entry and extended cranially and caudally about 2 cm. The tissues are dissected down to prevertebral fascia and a small pocket is created to anchor the lead. A 14G RX 2 Coudé (Epimed International, Dallas, TX) epidural needle (Fig. 2) is inserted in the direction of the contralateral inferior portion of the pedicle, with the aim of entering the epidural space in the midline (Fig. 1). Epidural entry is confirmed by a loss of resistance technique. The needle's curve is directed posteriorly to aid posterior epidural placement of the lead into the foramina (Figs. 1 and 3). An extended plastic introducer can be placed back into the needle to avoid dural puncture to change the direction of the bevel. This may be required to aid lead placement. We used a Linear ST Percutaneous Lead (Boston Scientific, Neuromodulation, Valencia, CA) 8 electrode subcompact lead of 31 mm with contact electrodes of 3 mm and edge-to-edge width of 1 mm and diameter of 1.3 mm (Fig. 4). The final lead position was such that the fourth and fifth electrodes covered the center of the proximal pedicle (Fig. 1 and 3). The lead position was confirmed with a

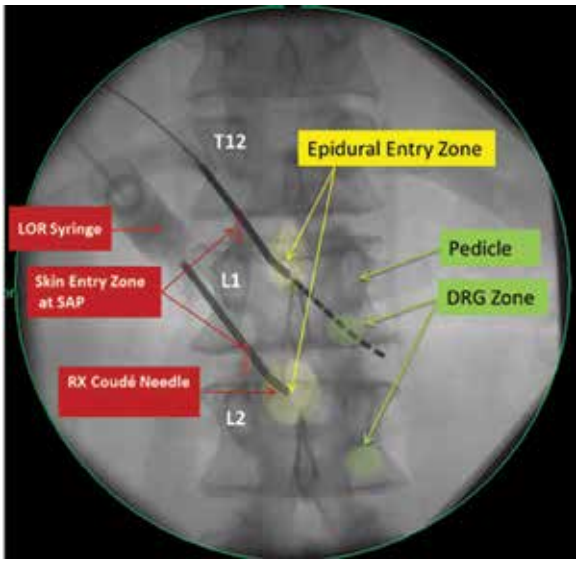

Fig. 1. *Transgrade technique under fluoroscopic guidance.*

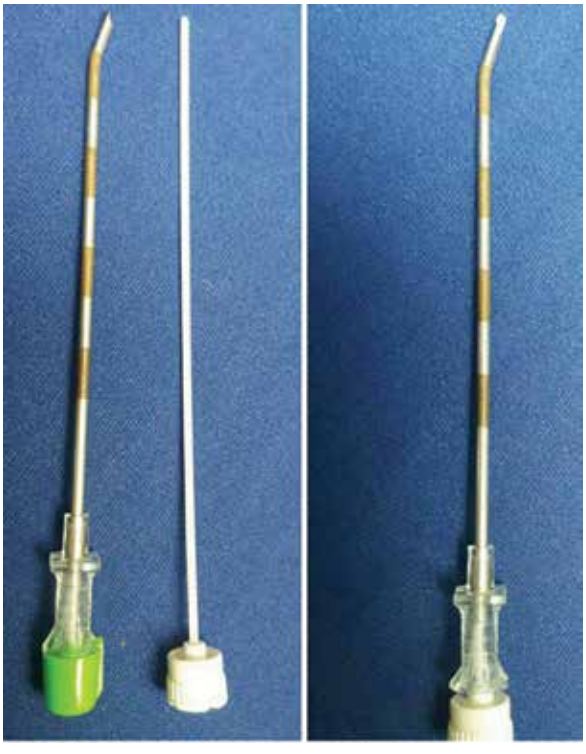

Fig. 2. *Racz Coudé needle.*

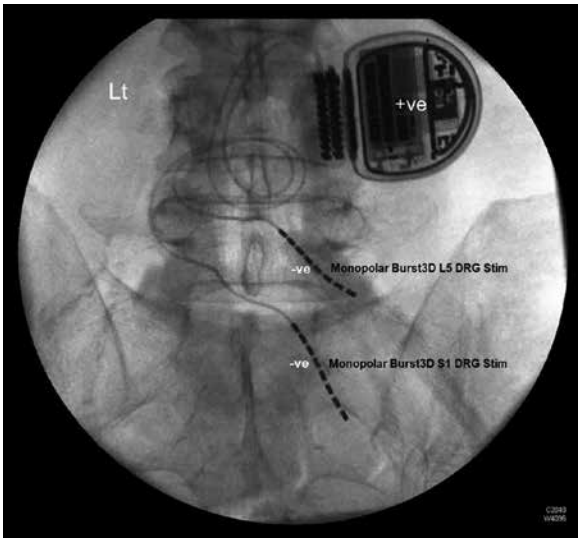

Fig. 3. *Right L5 and S1 DRG monopolar Burst-3D stimulation with cathode on the contact lead and anode on the IPG.*

Fig. 4. *Linear ST Percutaneous Lead, 8 active contacts, 1 mm edge-to-edge spacing, 31-mm span.*

lateral image to confirm lead placement into the dorsal foramina (Fig. 1). On-table low-frequency testing was performed in all patients to confirm comfortable paresthesia coverage of the painful area with no additional motor stimulation. The parameters of stimulation were a pulse rate of 70 Hz, pulse width of 150 μs, and incremental amplitude in steps of 0.1 mA using conventional tonic stimulation and a monopolar field with a single cathode on the lead and the anode on the IPG. Video of the technique is available at: https://www.youtube.com/watch?v=2qgUHM5SqNQ.

Anchoring

After removing the needle and stylet, the lead is secured to the lumbar dorsal prevertebral fascia with 2-0 Silk or a plastic anchor depending on the operator's preference. Extensions are then attached to the leads and tunneled out laterally where they are connected to an external pulse generator.

Trial

A 2-week trial period was conducted to determine the efficacy of stimulation. Patients who had a > 50% reduction in pain were offered a conversion to full implant. The complications documented included infection, hematoma, or lead migration.

Implant

Patients were fully implanted with a programmable IPG in a surgically created pocket either lateral to the paramedian incision or in the buttock.

Programming

The patients were programmed at initiation of the trial period with standard paresthesia testing to ensure the lead was covering the selected dermatome. The electrode directly under the pedicle was initially selected and adjusted to capture the maximum distribution of dermatomal pain. If the area of pain was not adequately covered, different electrodes were selected to ensure maximum efficacy. Reprogramming was then performed following full implant. Patients were programmed with a tonic subthreshold program and a burst program. The Burst-3D (Boston Scientific Neuromodulation) program consisted of 3 to 7 spikes of 500 Hz at 40 Hz using a pulse width of 500 to 1000 μs. The patients were followed up at 6 weeks, at which time further reprogramming was performed as needed. Any additional reprogramming after this period was documented.

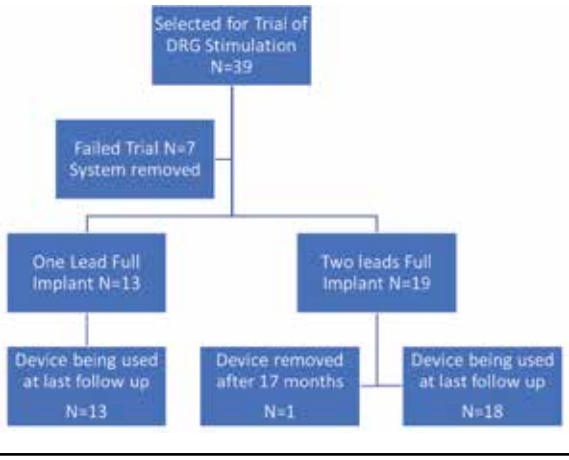

Fig. 5. *Patient CONSORT diagram.*

Table 1. *PGIC score template.*

PGIC Score	
1	No change (or condition has gotten worse).
2	Almost the same, hardly any change at all.
3	A little better, but no noticeable change.
4	Somewhat better, but the change has not made any real difference.
5	Moderately better, and a slight but noticeable change.
6	Better, and a definite improvement that has made a real worthwhile difference.
7	A great deal better, and a considerable improvement that has made all the difference.

Table 2. *Demographics of patients. Patients undergoing trial of DRG stimulation n = 39, full implant patients n = 32. Data are expressed as means with SEM and percentages.*

Mean age (SEM)	45.74 (± 2.126)
Gender	46% women (18 of 39)
Diagnosis	
	CRPS 49% (19 of 39)
	Ilioinguinal neuralgia 26% (10 of 39)
	Radicular neuropathic pain 10% (4 of 39)
	Neuropathic pain (knee) 5% (2 of 39)
	Phantom limb pain 5% (2 of 39)
	Testicular pain 2.5% (1 of 39)
	Peripheral neuropathy 2.5% (1 of 39)
Side of pain	
	Left 49% (19 of 39)
	Right 41% (16 of 39)
	Bilateral 10% (4 of 39)

Endpoints

The outcomes of this study were taken from a password-protected departmental database. An average weekly Numeric Rating Scale (NRS-11) score was taken (between 0 and 10) at baseline (before the trial period commenced) and after 6 weeks of stimulation following full implant. The patients were also asked to give their Patient Global Impression of Change (PGIC) score (Table 1), a 7-point scoring system. This had a stemmed question of, "Since starting DRG stimulation, how would you describe the change (if any) in activity limitations, pain symptoms, emotions, and overall quality of life related to your condition." Successful treatment with DRG stimulation was defined as having a PGIC score of 6 or 7, and a decrease of NRS-11 score > 2 from baseline before the trial period. Further follow-up was by telephone to determine the patient's up-to-date average weekly NRS-11 and PGIC scores. Complications as a result of the procedure or device were recorded in the database. Any complications related to the device were also inquired about if not documented on the database during telephone follow-up.

Statistics

Statistical analysis was performed on Prism Version 7 (GraphPad, San Diego, CA). Continuous data were expressed as means with standard error of the mean (SEM).

Data Collection

This was a retrospective case series over a 3.5-year period in a single tertiary referral center. These data were collected on a departmental password-protected database and updated during patient visits.

Results

A total of 39 patients underwent a trial of DRG stimulation of which 32 of 39 (82%) patients underwent a full implant (Fig. 5). The demographics of the patients are summarized in Table 2. The location of the leads placed are summarized in Table 3. CRPS was the most common indication for DRG stimulation in 19 of 39 (49%) patients. Out of the 7 patients who had removal of the system after the trial, 3 had CRPS, one had radicular neck pain following a surgical fusion, one had phantom limb pain, one had painful peripheral

Table 3. *Anatomic lead placement in n = 39 patients.*

Location of Lead	Number = 57
T1	2 (2%)
L1	11 (19.3%)
L2	3 (5%)
L3	7 (12.3%)
L4	4 (7%)
L5	19 (33.3%)
S1	12 (21%)

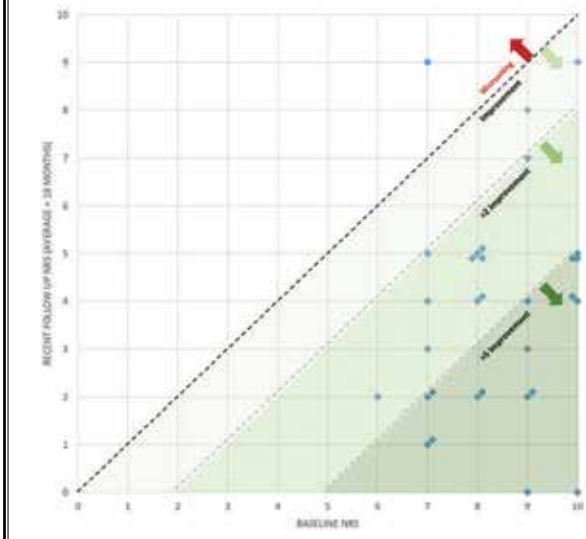

Fig. 6. *Change in NRS-11 from baseline at last follow-up (mean = 18 months).*

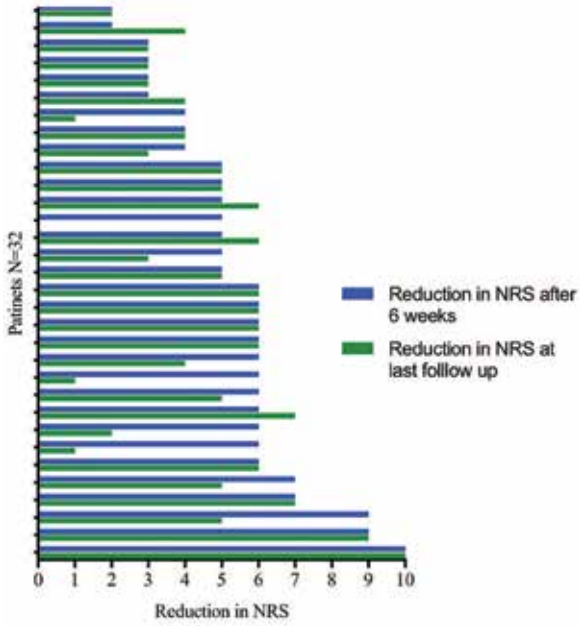

Fig. 7. *Reduction in NRS-11 at 6 weeks and last follow-up (mean =18 months).*

neuropathy, and one had ilioinguinal neuralgia. From the full implant cohort, 31 of 32 (97%) patients were using their DRG stimulators at last follow-up (mean of 18 months [SEM ± 1.8 months]). One patient had their system removed after 17 months on request due to lack of efficacy. This was despite having adequate coverage of the painful area and attempts at reprogramming. The rate of successful treatment, according to NRS-11 and PGIC scores, were 87% (28 of 32) at 6 weeks and 66% (21 of 32) at a mean of 18 months follow-up. Four patients were not contactable by telephone, therefore their last NRS-11 and PGIC scores were recorded at their last outpatient visit, which were 3, 4, 5, and 9 months prior to the dates of telephone review.

The change in NRS-11 score at 6 weeks and mean of 18 months are illustrated in Figs. 6 and 7. The PGIC score at 6 weeks and mean of 18 months is summarized in Fig. 8.

The preferred method of stimulation for the patients was the monopolar Burst 3-D protocol and was used by 25 of 32 (78%) patients. The number of patients who used a subthreshold tonic program only was 4 of 32 (12.5%), whereas 3 of 32 (9.5%) used a combination of the 2 (Fig. 9).

The complications are summarized in Table 4. Pocket pain was the most common device-related complication, seen in 7 of 32 (22%) patients. Three of the patients with pocket pain had CRPS, 3 had ilioinguinal neuralgia, and one had radicular neuropathic pain as a result of failed back surgery syndrome (FBSS). Two of the patients were managed conservatively with lidocaine patches, and 5 patients had their IPG site changed. Three of the patients had their initial IPG placement lateral to the paraspinal incision, and 2 had buttock placement. Lead migration rate was 5.2% (3 of 57 leads placed). The rate per patient was 8% (3 of 39) of which one occurred during the trial period and the other 2 following full implant of the IPG. In all 3 cases, the lead had to be fully revised as it had come out of the neuroforamen. Reprogramming was required in 9 patients (9 of 32, 28%) after 6-week follow-up. The cause and outcomes are documented in Table 4.

Table 4. *Complications related to implantation. Patients undergoing a trial of DRG stimulation n = 39, full implant patients n = 32, leads placed n = 57.*

Complication	Number	Outcome
Pocket pain	7 of 32 (22%)	5 cases site was changed, 2 managed conservatively with lidocaine patches
Lead migration	3 of 57 (5.2%)	All leads revised
Infection	1 of 39 (2.5%)	System removed and later replaced
Wound hematoma	1 of 39 (2.5%)	Surgically evacuated
Required reprogramming (excluding lead migration)	9 of 32 (28%)	
Overstimulation	4 of 9	Reduced amplitudes
Poor coverage	2 of 9	Parameters changed
Reduced efficacy	1 of 9	Parameters changed/ explanted
Reduced efficacy	1 of 9	Switched from tonic to burst
Device switching off	1 of 9	Education given

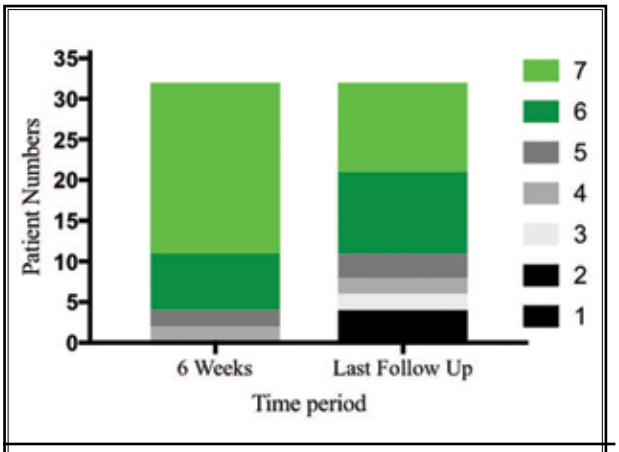

Fig. 8. *PGIC score after 6 weeks and at last follow-up (mean = 18 months).*

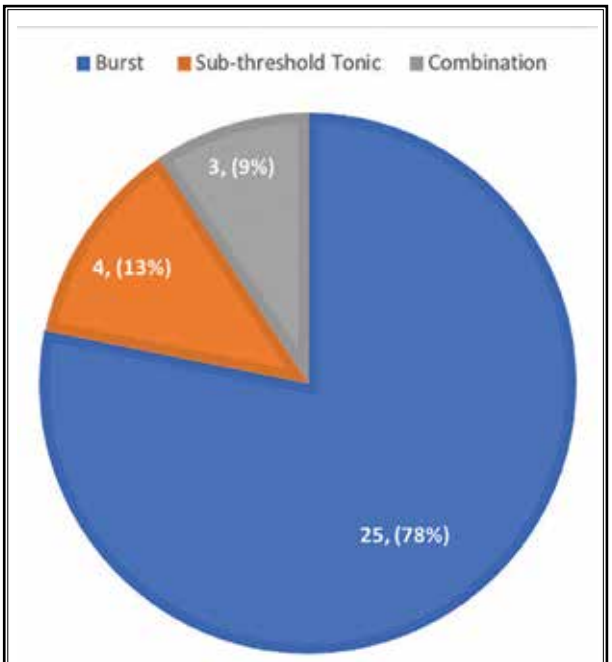

Fig. 9. *Method of stimulation used in patients implanted (n = 32).*

Discussion

We present a novel technique for epidural placement of leads for DRG stimulation. Similar approaches have been previously reported but with a more retrograde angle and the addition of a laminotomy and stylet to target the neuroforamina (44,45). The needle position is also not midline in this approach, and relies on the stylet to guide the lead into position (44). A more horizontal approach has also been reported in the consensus guidelines (24). Aside from the Racz Coudé (Epimed International) needle this technique does not require any specialist hardware and can be used with any compact lead of similar dimensions as described. This gives the ability to combine DRG and SCS stimulation with the same IPG and multiple programming options, potentially improving patient outcomes. There has been a trend to greater use of novel waveforms for SCS due to improved efficacy in patients with FBSS including BurstDR (Abbott, Plano, TX) (46-52). The diversity of waveforms now available has not necessarily phenotyped specific pathologies to waveform; patients with CRPS favor different modes of stimulation (47). We highlight that the majority of patients preferred a different program to conventional tonic stimulation over the DRG. By incorporating this technique in different systems other waveforms can be used, which are largely paresthesia free.

Safety

There were no adverse events related directly to the Transgrade entry and placement of the leads, and no incidence of nerve trauma in this case series. Cases of neurologic symptoms after trials or full implants of DRG stimulation, using an approach different from the trans-

grade approach described here, appear to be higher than previously reported from a recent publication by Sivanesan et al (53). This result needs to be taken with caution, however, as their classification of "neurologic symptoms" may have been mistaken for painful stimulation (53). Recent data have also concluded that safety is equivalent between SCS and DRG stimulation devices from the same manufacturer (54). There is a consensus point within the appropriateness of best practices for DRG stimulation in relation to the introduction of the guidewire and sheath that may lead to nerve irritation (24). Our technique described does not involve this step as the path of the needle is more parallel to the foramina, allowing the lead to anatomically follow the nerve. The diameter of the leads used in this case series is 1.3 mm, which is 0.3 mm wider than the Axium Neurostimulator System Slim Tip (Abbott, Plano, TX) used for DRG stimulation in other studies (28). We did not encounter any difficulty inserting the leads into the foramina using a larger lead. The dimensions of the foramina from an anatomic study were a median diameter of 8.8 mm in the lumbar spine, with the most narrow point recorded of 3.3 mm (55). Excluding any foraminal stenosis, this is unlikely to be a problem with the leads used in this case series. None of the patients in this study presented with loss of disc height from degenerative changes or previous surgeries, nor were any patients noted to have unstable spondylolisthesis, 2 anatomic conditions that are relative contraindications to use of this technique at those specific neuroforamina. There were no incidences of dural puncture within this series. A theoretical increased risk of dural puncture with DRG lead insertion has been attributed to the sheath and guidewire and extensive manipulation to obtain foraminal access (53). In our series, the risk of dural puncture diminished likely with the use of the second plastic stylet of the Racz Coudé 2 (Epimed International) needle during bevel redirection. As the leads were anchored, this potentially lead to a low incidence of lead migration (56). Leads in other publications were not always anchored; a strain relief loop is often created to minimize the incidence of lead migration (24,28,57).

Analysis of Transgrade Technique

Once the needle bevel crosses the midline as described (Fig. 1), the lead is trajected to enter the neuroforamina parallel to the spinal nerve root. Maneuverability can be controlled by rotating the lead and changing the bevel angle of the RX Coudé (Epimed International) epidural needle. We prefer to angle the bevel of the needle posteriorly to ensure posterior placement of the lead. In our experience, there are multiple potential paths that the lead will follow after passing through the initial neuroforaminal ligaments. The consensus guidelines using the Abbott system recommends aiming toward the inferior medial border of the pedicle to stay in the superior part of the foramen, to minimize displacement (24). This can be easily achieved with the Transgrade technique. As there is a paucity of evidence available on the exact location of the DRG at different levels, on-the-table stimulation likely remains the best method of ensuring accurate lead placement (58-60). One must also consider that the DRG can be intraspinal or extraforaminal, and there are no specific guidelines on how to determine which is the case without 3-dimensional fast field echo with water selective excitation and coronal magnetic resonance imaging (MRI) reconstructed DRGs (59). Our lead placement covers the zone where the DRG can be found. In a case series of 115 healthy volunteers, 5.3% of L5 DRGs were located at an intraspinal location (59). Biganglia (2 DRGs) were also reported at L3 and L4 in the same study up to 50% of the time, with triganglia having an incidence of < 1% (59). The relation of these variances to the success or failure of DRG stimulation still remains undetermined; perhaps performing an MRI scan with coronal sections to determine the size, shape, and location of the effected DRG in relation to the pedicle may be prudent.

Efficacy

The use of monopolar stimulation theoretically should give a precise, more accurate target area, but we are unable to determine its superiority or inferiority in this study. Monopolar stimulation with tightly spaced electrodes may enable close stimulation of the DRG without spill over, which may occur with a bipolar array. Our successful outcomes are lower than some quoted in the literature, but we have used different criteria, focusing on a multidimensional outcome of PGIC score (28). The mean follow-up time of 18 months in this study is longer than those quoted in the literature (23,25). We have also demonstrated that there are a cohort of patients who initially respond, but the efficacy of DRG stimulation reduces over time. The incidence of overstimulation occurring during DRG stimulation in the ACCURATE study was reported to be 3.9%, but no details were given of how this was managed (28). Our rate of overstimulation (4/32, 12.5%) is higher than what is quoted in the literature, but it resolved

after reprogramming. Reprogramming was required beyond 6 weeks in other cases, but only one case ended in explant. Lost efficacy cannot always be retrieved by reprogramming even in the absence of lead displacement (61). The reasons for this are likely multifactorial and we currently have a lack of understanding of why patients lose efficacy (56,61,62). Pocket pain was prevalent among our patient cohort in different IPG positions; this may be related to the size of the battery that has been described as a contributing factor (56). Another contributing factor could be patients having CRPS as a diagnosis, predisposing them to persistent pain following surgical nerve trauma during IPG placement. Within the ACCURATE study, the incidence of pocket pain was lower at 13.2%, but 7.9% of patients complained of persistent pain at the incision site (28). There is still much debate over the best location for IPGs when implanting patients with chronic pain.

Limitations

Because of the retrospective nature and small sample size, this review has limitations. Although we have used PGIC as an outcome, we lack many other multidimensional outcomes. The results at last follow-up were also conducted over the telephone in the majority of patients, which also carries limitations.

Conclusions

The Transgrade technique of placing DRG leads offers an alternative technique that is safe and effective. This technique can also be used for lateral nerve root stimulation. There is a learning curve as with any new procedure, and we would only recommend practitioners use this method after a period of training. The comparative efficacy of monopolar contact electrodes for DRG stimulation remains to be determined. There is still no clear evidence that the DRG is the structure precisely targeted when referring to "DRG stimulation," owing to a lack of visualization of the DRG proper during implantation. It is most likely intraoperative electrophysiological testing will be needed to appropriately determine optimal anatomic field proximity to the DRG for the purposes of neurostimulation therapy. The use of multiple independent current control will be needed to facilitate this type of testing, not heretofore available for DRG therapy.

This case series illustrates that patients favor different methods of stimulation, and the majority of our patients preferred the burst paresthesia-free waveform for their therapy. The use of burst stimulation to the DRG will need to be assessed formally, however, in a randomized controlled trial that is under way (ClinicalTrials.gov identifier: NCT03318250). The future of DRG stimulation continues to evolve, and a variety of techniques and modalities of stimulation will likely benefit patients with chronic neuropathic pain. The use of new devices and stimulation programs also remain to be explored for DRG stimulation.

Acknowledgments

The authors would like to thank Andrea Trescot, MD for reviewing the article prior to submission, and for her input on the project.

Authors contributions: Adnan Al-Kaisy designed the technique. Adnan Al-Kaisy, Stefano Palmisani, and David Pang carried out the procedures. Jonathan Royds, Matteo Costanzi, and Samuel Wesley collected the data and carried out analyses. Jonathan Royds, Adnan Al-Kaisy, Gabor Racz, and Thomas Yearwood drafted the article. All authors reviewed the article prior to submission.

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