DOI: 10.1111/papr.13113

RESEARCH ARTICLE

Dorsal root ganglion stimulation device explantation: A multicenter pooled data analysis

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Funding information
No funding was received for this work.

Abstract

Introduction: Dorsal root ganglion stimulation (DRG-S) is a relatively new neuromodulation modality. Therefore, data on long-term device explantation rates is limited. This investigation aimed to assess DRG-S device explantation rates at long-term follow-up.

Methods: We retrospectively reviewed individuals implanted with DRG-S in four pain centers from different continuous periods between April 2016 to September 2020. We recorded patient demographics, diagnoses, duration to explantation or last follow-up, treatment complications, and failure etiologies.

Results: A total of 249 patients with 756 leads and a mean 27-month follow-up were included. The mean age was 55 ± 15 years; 148 (63%) were female. Leading diagnoses were CRPS (n = 106, 43%), followed by FBSS (n = 64, 26%), and non-surgical low back pain (n = 23, 9%). The explantation rate was ~2% per year (n = 10 total). At explantation, the average time from implantation was 13 ± 10 months. Six patients were explanted for inadequate pain relief. Two patients were explanted due to device-related complications. One patient was explanted secondary to infection and subsequently reimplanted. Five explanted patients experienced a therapy-related complication before eventual explantation: one transient post-procedural neuritis and pocket site pain, one lead fracture, two lead migrations, and one experienced a fracture, a migration, and pocket site pain.

Discussion: This large retrospective study of DRG-S revealed a low therapy-termination rate. The rate of infection leading to explantation was objectively very low at 0.4%. The leading cause of explantation was inadequate pain relief. Explanted patients often had a therapy-related complication. Therefore, minimizing adverse treatment events may reduce ultimate explantation rates.

INTRODUCTION

Dorsal root ganglion stimulation (DRG-S) has effectively treated complex regional pain syndrome (CRPS) and causalgia since it became commercially available in the United States in 2016.[1] Over the last 5 years, retrospective studies continued to reveal a broader real-world physician and patient experience, providing essential clues to improve DRG-S outcomes and durability that were inapparent or unfeasible to study in controlled

clinical trial designs.[2] The fundamental similarity between spinal cord stimulation (SCS) and DRG-S – placing a flexible electrode, energized by an implantable pulse generator (IPG), over a neuronal target accessed via the epidural space – invites a comparison of the two modalities.[3] Implantable device complications are generally categorized as device-related, biological, and diminished efficacy.[4] Leaning on the prior SCS experience, neuromodulators began to recognize DRG-S lead positional stability,[5] lead fracture,[6] infection,[7] and tolerance prevention as the cornerstones of therapeutic longevity.[8] Compared to the SCS literature, DRG-S evidence maturity is in an early, active development phase.

The primary aim of the present study was to investigate the device explantation rate in a large sample of patients implanted with DRG-S. A secondary purpose was to evaluate the underlying causes of device explantation and to determine if any therapy-exit predictors could be derived from examining the explanted patients' demographic and clinical factors.

METHODS

The inclusion criteria for this study were: all consecutive adult patients permanently implanted with DRG-S systems (Proclaim or Axium system, Abbott, Plano, TX, USA) between April 1st, 2016, to September 30th, 2020. We included patients implanted for any indication. Although DRG-S is currently approved by the United States Food and Drug Administration to treat chronic neuropathic pain associated with CRPS and/or peripheral causalgia, in clinical practice, it is applied in a broader patient population. Therefore, we intentionally designed our analysis to be reflective of the real-world explantation rate of DRG-S.

Institutional Review Board approval (IRB#: i20-01409) or waiver was obtained before commencing the retrospective analysis. Two institutions collected data under the IRB protocol and two institutions provided anonymized data under a data sharing agreement, since they had already collected the data in the context of other IRB-approved research. The data was collected from patients implanted with DRG-S from 2016 to 2020 in four centers in the United States. The including centers consisted of two large academic centers and two large private interventional pain management practices with academic affiliations. Geographically the including centers were situated in cities of varying size in the eastern US with catchment areas extending beyond city limits. The implanters were three interventional pain physicians and a functional neurosurgeon. All were experienced with SCS implantation surgery, as defined by implanting more than 25 systems per year,[9] and had undergone additional training for DRG-S implantation. All patients underwent 5-to-7-day external trials with DRG-S. Definitive implantation was offered to patients who experienced pain relief of 50% or more during the trial period.

All definitive implantation procedures were performed in an operating room. The four investigators used the contemporary implant technique for lead placement.[10,11] This approach starts with a needle puncture at the lateral aspect of the pedicle, two levels below the target foramen using a contralateral method. Epidural strain relief loops are placed in an "S" configuration with multiple loops in the inferior and superior aspects of the "S". The IPG is placed in the gluteal region.

After implantation, follow-up consisted of an initial postop visit within 7 days of surgery followed by a 1-month visit and as needed visits for any programming or complication issues. Patients were seen by the implanting provider and/or a fellow, or advanced practice provider depending on the type of visit, with or without a device representative to assist in patient programming. Many patients were followed monthly for medical management and were seen on a regular basis. However, there was no specific follow-up in the context of research to systematically assess explantation. Considering this was a large retrospective study of real-world explantation data, there was no standardized treatment algorithm indicating when explantation would occur. The decision to explant a system was always a patient-centered decision, which was made by shared decision making after all options to salvage DRG-S therapy efficacy had been exhausted.

Patient demographics, diagnoses, and lead location were presented using descriptive statistics for all patients and explanted patients. DRG-S system explantation was the primary outcome of this study and was graphed using reverse (failure) Kaplan–Meier curves with a pointwise 95% confidence interval. Survival was censored at the end of the observation period or when patients withdrew from the center where they were implanted. Statistical analyses were performed using JMP Pro (version 15).

We previously analyzed data from this sample to assess if DRG-S lead anchoring can prevent lead migration, and these results have been published.[6]

RESULTS

A total of 249 patients with 756 leads were included and inclusion by individual center is displayed in Figure 1. Demographic and clinical data are presented in Table 1. The mean patient age was 55 ± 15 years. The most common primary diagnoses were complex regional pain syndrome (n = 106, 43%), failed back surgery syndrome (n = 64, 26%), and non-surgical low back pain (n = 23, 9%). Across all patients, the median duration of follow-up was 790 days. Follow-up duration was censored for patients withdrawing from care at the center where they were implanted in 12 cases (5%). Two of these patients left care because they moved out of state, for the remaining 10 cases we were unable to ascertain the reason for

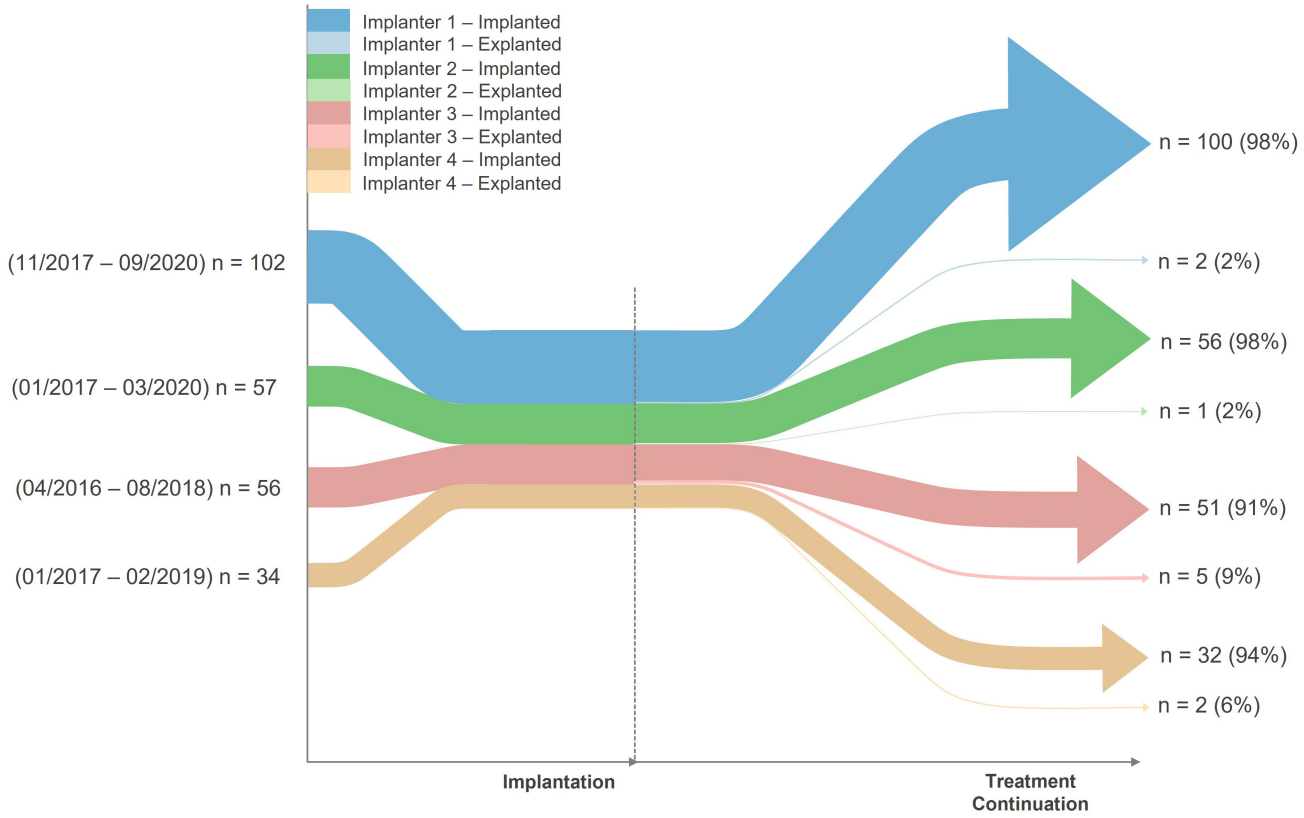

FIGURE 1 Sankey diagram of implantations and explantations by contributing center. Flow of patients from each contributing implanter is depicted by lines connected to treatment continuation outcome (explanted or not explanted). The width of each line is proportional to the number of patients. The exact implantation periods for which individual implanters provided data are provided for the implantation phase (left). Explantation percentages (right) in the treatment continuation phase are based on the denominator of patients implanted by each implanter

leaving care. To our knowledge, all patients withdrawing from care had functioning DRG-S systems at the point of withdrawal.

Explantation occurred in 10 patients. Explantation risk over time with a 95% confidence interval in the entire cohort is presented in Figure 2. Estimated probability of explantation was 2.5% (95%-CI: 1.1%–5.4%) at 1 year, 4.4% (95%-CI: 2.3%–8.4%) at 2 years, 5.4% (95%-CI: 2.8%–10.1%) at 3 years, and 5.4% (95%-CI: 2.8%–10.1%) at 4 years post-implantation. Demographic and clinical characteristics of explanted patients are presented in Table 2. The explantation that happened at the longest period since implantation was performed at 30 months. Nine out of 10 explanted patients were female. The most common indication for DRG-S therapy in explanted patients was CRPS (n = 7/10).

Device-related complications

We previously reported on the lead migration and lead fracture rates in this cohort[6]; lead migration occurred in 18 patients whereas lead fracture occurred in 15 patients. Therapy efficacy was restored in all but two patients. Patient 2 was explanted because she did not experience restoration of therapy efficacy after a revision for lead migration (Table 2). Patient 7 opted to convert to SCS after experiencing a lead fracture. She previously had undergone revision for a migrated lead.

Biological complications

One patient (Patient 8) was explanted secondary to infection and subsequently reimplanted (Table 2).

Diminished efficacy

Six patients were explanted for inadequate pain relief. One patient experienced a resolution of pain leading to explantation (Patient 6, Table 2). Of the six patients explanted for inadequate pain relief, three experienced a gradual decline of effect (Patients 3, 5, 10). Three patients (Patients 1, 4, 9) who were explanted for inadequate pain relief did not experience the conventional pattern of development of loss of efficacy after a period of good pain control but did not ever have satisfactory pain relief

TABLE 1 Demographic and clinical characteristics of all implanted patients

	Implanted patients (n = 249)
Age at implantation in years, mean ± SD	55 ± 15
Sex in female/male, n/n (%/%)	153/96 (61/39)
Body mass index in kg/m^2, mean ± SD	31 ± 5
Primary diagnosis, n (%)	
Complex regional pain syndrome	106 (43)
Failed back surgery syndrome	64 (26)
Non-surgical low back pain	23 (9)
Peripheral neuropathy	12 (5)
Joint pain	10 (4)
Dermatomal neuropathic pain	12 (5)
Radiculopathy	9 (4)
Peripheral vascular disease	2 (1)
Abdominal/pelvic pain	10 (4)
Sacroiliac joint pain	1 (0.4)
Vertebral level of leads placed, n of patients (%)[a]	
C4-C8	9 (4)
T1-T2	4 (2)
T7	1 (0.4)
T9-T11	5 (2)
T12	110 (44)
L1	26 (10)
L2	22 (9)
L3	35 (14)
L4	63 (25)
L5	58 (23)
S1	152 (61)
S2	9 (4)
S3	2 (1)
Time to last follow-up in days, median (IQR)	790 (447, 1110)

[a]n and % across all levels is greater than total number of patients because leads can be located at multiple levels within the same patient.

after initiation of DRG-S with their permanent implant, even though all patients experienced significant pain relief during their trial stimulation period. Two explanted patients with diminished efficacy experienced therapy-related problems before eventual explantation: one experienced transient post-procedural neuritis and pocket site pain (Patient 1, Table 2) and one had a lead fracture (Patient 5, Table 2). Patient 5 underwent surgical revision whereas Patient 2 was managed conservatively. The therapy-related complications in these patients did not lead to explantation directly, but rather appeared to have contributed to an overall ineffective therapy course and ineffective relief of pain with DRG-S over time. We did not observe any patients who decided against explantation and opted to leave their DRG-S device in-situ while turned off.

DISCUSSION

Principal findings

As clinical experience with DRG-S increases, knowledge on long-term complication rates inevitably follows.[12–15] This large, real-world, retrospective study on DRG-S reveals an objectively low explantation rate (~2%/year). Inadequate pain relief was the underlying reason for six explantations, while device-related complications led to two explantations, and one patents was explanted due to infection. One patient was explanted after her pain disappeared. Patients who experienced a well-defined therapy-related complication were more likely to exit therapy through explantation.

Overall explantation rate – prior DRG-S studies

In the initial landmark ACCURATE randomized controlled trial comparing DRG-S to SCS for CRPS, there were no explantations in the 76 patient DRG-S cohort.[1] On the other hand, a pooled analysis of 256 implants reported an explantation rate of 3.1%, excluding infectious causes.[16] Our DRG-S study cohort of 249 implanted patients underwent an overall ~2% per year and a 4% rate of explantation over 27 months which thus seems consistent with previously reported longer follow-up studies in real-world settings.

DRG explantation due to device-related complications and inadequate pain relief – prior DRG-S studies

Two patients were explanted directly due to device-related complications (a lead migration and a lead fracture) and six patients were explanted for inadequate pain relief. In two patients explanted due to inadequate pain relief, prior complications had occurred; one experienced transient post-procedural neuritis and pocket site pain and one had a lead fracture. The patient with the lead fracture had revision surgery prior to eventual device explantation. Patients experiencing a surgical complication are more likely to experience a second complication[17] and have worse outcomes with surgery,[18] as did our cohort. Surgical revision may be complicated by epidural fibrosis[19,20] and lead to suboptimal placement in addition to the increased risk of neurologic sequela after repeated attempts at lead placement.[15] Reducing migration through lead fixation should lessen the risks associated with revision surgery and could potentially decrease explantations.[6] IPG pocket site pain is an often under-reported adverse event. In a pooled analysis of 217 patients with permanent DRG-S systems, the investigators detected 26 pocket pain occurrences, and the ACCURATE study reported 11 complaints of pocket

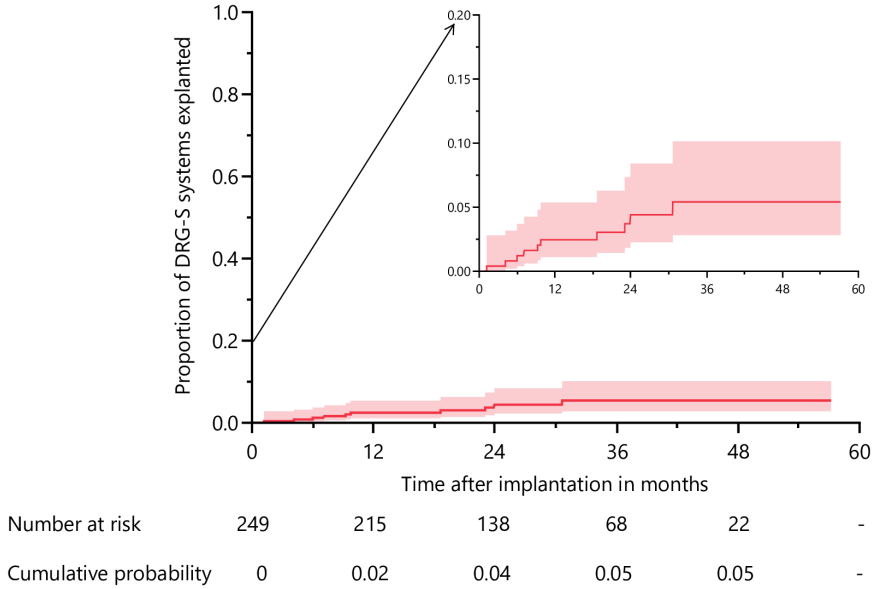

FIGURE 2 Reverse Kaplan–Meier curve of overall dorsal root ganglion stimulation system explantation. The shaded area represents the pointwise 95% confidence interval of the cumulative failure probability. Figure inset shows axis magnifications

site pain in 76 patients (14.5%).[1,21] As with other implantable therapies, DRG-S implant site pain is a common complaint, primarily handled conservatively.[22–24]

A potential factor leading to a low rate of explantation due to inadequate pain relief in this study could be that the four implanters in the present study were relatively experienced with DRG-S post-implantation care, particularly with programming optimization. Considering the narrow subthreshold stimulation therapeutic window with DRG-S, patients may fall to sub-therapeutic levels or over-stimulate relatively easily, leading to pain and suboptimal outcomes. Patient education and reprogramming vigilance can mitigate the above challenges.

DRG explantation due to infection among prior DRG-S studies

This study found an infection rate of 0.4% as the underlying reason for device explantation. A pooled review of six Dutch DRG-S studies revealed 13 infections in 217 implanted patients over 12 months (6.0% per annum), which is higher than the rate we encountered. An analysis of their infections with DRG-S demonstrates that four were treated conservatively with antibiotics, seven were documented to be explanted, and two were unspecified.[16] Their explantation rate related to infection thus was in the range from 3.2%–4.1% ($n = 7$ or $n = 9/n = 219$). Over 2 years, the aforementioned post-market analysis, including 500 DRG-S devices, reported a 1.08% infection rate.[3] Therefore, our encountered rate of infection leading to therapy termination (0.4%) was lower than previously reported rates.

Due to the consecutive patient selection design, we negated that our cohort somehow had a lower burden of established risk factors, such as diabetes, poor nutritional status, smoking, use of corticosteroids, chemotherapy, and radiation therapy.[18] A plausible explanation for a low infection rate in our study was the consistent treatment of pre-operative *Staphylococcus aureus* colonization and the use of postoperative antibiotic prophylaxis. Additionally, we performed a 5 to 7-day trial separate from the definitive lead and IPG implant date, a practice distinct from the extended trial, which is more commonly performed in Europe. In the context of SCS, North et al.[25] recently demonstrated that a trial duration of more than 10 days was correlated with a 24% rate of infection among ensuing implantations. The above findings may explain the increased European infection rates, illustrated by an 8.5% infection rate in a study where trials lasted up to 30 days.[26]

Overall explantation rate comparison DRG-S to SCS

Dorsal root ganglion stimulation is often considered as a relatively novel alternative to SCS. Therefore, it is crucial to contextualize the DRG-S explantation rates against the existing SCS explantation data. Overall SCS explantation rates are reported to range from 3.1% to 11.1% per year[27–29] and from 7.6% to as high as 32.5% over extended time intervals.[4,29,30] Improvements in SCS technique,[31,32] improved anatomic localization for lead placement,[33,34] and technological advances have reduced SCS overall explantation rates. However, the overall device explantation rates have only slightly improved over time[4,35,36] and remain as high as 11% per year in recent studies.[29] The overall explantation rate of ~2% per year that we found is thus lower than typical SCS explantation rates.

TABLE 2 Demographic and clinical characteristics of patients ($n = 10$) who underwent DRG-S device explantation

Patient	Age at explantation (years)	Sex	Diagnosis	Lead location	Reason for explantation	Prior complication?	Time to explantation (months)
1	24	F	CRPS type 2	T11, T12, L1	Diminished efficacy	Transient neuralgia and pocket site pain.	3
2	64	F	FBSS	T12, S1	Device- related complication	S1 migration	4
3	67	F	CRPS type 2	S1	Diminished efficacy	No	9
4	46	M	CRPS type 1	L2, L3, L4	Diminished efficacy	No	18
5	65	F	CRPS type 1	L4, L5	Diminished efficacy	L5 fracture	30
6	41	F	CRPS type 1	L4, S1	No longer pain	S1 migration	23
7	43	F	CRPS type 1	C7, C8	Device- related complication	1 migration, 1 fracture, pocket site pain	23
8	56	F	CRPS type 1	L3, L4, L5	Biological complications	No	1
9	53	F	Neuropathy	L5, S1	Diminished efficacy	No	5
10	57	F	FBSS	T12, S1	Diminished efficacy	No	12

Abbreviations: CRPS, complex regional pain syndrome; FBSS, failed back surgery syndrome.

Explantation rate due to inadequate pain relief comparison DRG-S to SCS

Loss of efficacy is a well-known but poorly understood process that has been shown to affect all forms of SCS, leading to SCS explantation rates from as low as 1.7% to 4.2% per year to up to 20.3% explanted over 22 months.[27,28,36–38] The rate of inadequate pain relief leading to explantation we encountered (~2%) is low compared to rates reported for SCS. In the context of SCS, loss of efficacy is generally defined as the failure of a neuromodulatory therapy's effects over time while maintaining adequate lead positioning. Loss of efficacy has been proposed to be related to habituation and a physiological desensitization due to prolonged, repetitive stimuli exposure where an escalated dose is needed to elicit the same effect. However, increasing electrical dose does not always restore the effects of neuromodulation and can potentially result in unwanted stimulation, side effects, pain, and potentially accelerated loss of efficacy.[39–41] High electrical doses have been theorized to cause neuroplastic damage,[42] including in the dorsal horn and other neuronal transmitter synthesizing regions of the spinal cord that are important for pain modulation through glutamate and gamma-aminobutyric acid (GABA) circuitry.[43] Levy et al.[8] concluded that DRG-S might be less prone to habituation than SCS in an ACCURATE study sub analysis. DRG-S has been demonstrated to affect alternative non-GABA mediated mechanisms in the dorsal horn.[12,14,44] It has been proposed that the endogenous opioid system plays an underlying role in DRG-S efficacy.[14,44] While such a mechanism is ostensibly at risk for opioid receptor internalization, the process believed to underlie the development of tolerance to opioid medications,[45] internalization rarely occurs when receptors are activated by endogenous opioids, as opposed to the rapid internalization that occurs with exogenous opioid activation.[46] Of interest, in the present study three patients who were explanted for inadequate pain relief did not experience the conventional pattern of development of loss of efficacy after a period of good pain control, but did not ever have satisfactory pain relief after initiation of DRG-S with their permanent implant. The different mechanisms of action of SCS and DRG-S may underlie these different trajectories of inadequate pain relief from therapy.

Of interest, five out of six patients who underwent explantation for inadequate pain relief were women. Female sex has been shown to be a risk factor for SCS device explantation.[9,27,38,47] It has been postulated that there may be differences in pain modulation or inhibition of painful stimuli between men and women, with women having less efficient inhibition of noxious stimuli than men.[48] However, there may also be gender-based differences in the expression or behavioral response to pain. Much of the current research on sex differences is difficult to extrapolate to clinical settings.[49]

Another factor to consider is that DRG-S uses a non-rechargeable, primary cell, IPG, and this has been shown to be protective against device explantation.[27,50] We hypothesize that the convenience of not having to charge a device improves therapy success.

Explantation rate due to infection comparison DRG-S to SCS

A national Medicare review of 12,297 SCS implantations between 2005–2014 revealed a 4.3% infection rate at 1 year.[51] Infection as a cause of SCS device explantation has ranged in the literature from ~2.4%[28,30,37] to 10%,[52] with most studies clustering around 4%–6%.[36,51,53–55] The infection rate of 0.4% we encountered is thus much lower than rates previously reported with SCS. We hypothesize that increased physical activity with DRG-S may contribute to lower infection rates when compared to SCS. Early ambulation to decrease postoperative infections is an accepted practice that has repeatedly been demonstrated in systematic reviews.[56,57] DRG-S has demonstrated greater improvements in physical function, as measured by disability scores,[21,58–62] compared to SCS.[63–65] Robust improvements in functional status may thus relate to low infection rates. Additionally, DRG-S has effects on the sympathetic nervous system and neurogenic inflammation.[66,67] The inhibitory effects of DRG-S on the sympathetic nervous system and neurogenic inflammation may have helped prevent infection. However, our understanding of these mechanisms remains limited.[68–72]

Limitations

Several limitations pertain to this study. First, as a retrospective multicenter study, DRG-S surgical techniques were not standardized. Second, a small proportion of patients withdrew from follow-up and we could not ascertain their status. Third, since surgical experience is related to lower complication rates,[73] one could conclude that implanter experience contributed to low explantation rates. However, in a Market Scan database review, medium volume SCS implanters (9–24 implantations/year) had a lower explantation rate than low and high-volume implanters.[9] The four implanters in this study would be considered as high-volume implanters. Fourth, in the cohort we did not observe any patients who decided against explantation and opted to leave their DRG-S device in-situ while turned of; however, it is possible that some patients did not use their implanted device much. It is challenging to reliably collect stimulation history data from DRG-S devices and we thus did not attempt to probe this question specifically. Fifth, we originally attempted to assess factors related to explantation; however, confronted with low explantation rates we had insufficient statistical power to assess individual explantation causes statistically beyond descriptive statistics. Additionally, the exact periods of inclusion varied by center (Figure 1) as a result of different ethical review board approvals for different centers. Finally, the median follow-up in the present cohort is not as long as for some previously published SCS cohorts.[4,9] We intend to perform further follow-up on this group of patients to assess whether explantation rates remain low over an even longer follow-up period.

CONCLUSION

Dorsal root ganglion stimulation is associated with an objectively low explantation rate (2%/year) when compared to previously reported explantation rates for SCS. Most systems were explanted because of inadequate pain relief. Explanted patients often have a DRG-S therapy-related complication before undergoing ultimate device explantation. Infection is a rare underlying cause for explantation. Further technology and surgical techniques improvements to reduce complications may further reduce ultimate device explantation rates.

ACKNOWLEDGEMENTS

The authors thank Allison Foster, PhD, an independent medical writer, for her editing assistance. TL would like thank research assistant Lauren Kret for assisting in data collection.

CONFLICT OF INTEREST

Jan Willem Kallewaard is on the advisory board Abbott, Saluda, Nevro, Boston Scientific. Timothy Deer is a consultant for Abbott, Medtronic, Boston Scientific, Nevro, Nalu, Saluda. He has equity in Saluda, SPR, Spinethera, Nalu, Cornerloc, Paintec and Vertos. Research funding with Boston Scientific, Abbott, Saluda. Alon Mogilner is a consultant for Abbott Medical and Medtronic, and has received fellowship funding from Abbott and Medtronic. Timothy Lubenow is a consultant for Abbott, Boston Scientific, Medtronic, Nevro, Avanos, and Flowonix. Research funding with Abbott, Boston Scientific, and Nevro. Kenneth Chapman, Ajax Yang, and Noud van Helmond have nothing to disclose.

AUTHOR CONTRIBUTIONS

KBC, AYM, AY, TL, and TD collected data. KBC, AY, and NvH prepared the majority of the manuscript with important intellectual input from all authors. NvH verified the analytical methods and performed statistical analysis. All authors approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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How to cite this article: Chapman KB, Yang A, Mogilner AY, Mandelberg N, Patel KV, Lubenow T, et al. Dorsal root ganglion stimulation device explantation: A multicenter pooled data analysis. Pain Pract. 2022;00:1–10. https://doi.org/10.1111/papr.13113