Dorsal Column Stimulation vs. Dorsal Root Ganglion Stimulation for Complex Regional Pain Syndrome Confined to the Knee: Patients' Preference following the Trial Period

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ABSTRACT

Background and Objectives: Patients with complex regional pain syndrome (CRPS) confined to the knee are often therapy resistant. Neurostimulation is an accepted treatment for CRPS. Although results with dorsal column (DC) stimulation in patients with CRPS confined to the knee are often disappointing, the availability of dorsal root ganglion (DRG) stimulation may provide new opportunities for this complaint. Therefore, this study explores patients' preference for DC stimulation versus DRG stimulation in treating chronic pain due to CRPS confined to the knee.

Methods: A prospective, observational crossover cohort study was conducted comparing 2 methods of neurostimulation, in randomized order, in patients with CRPS confined to the knee. After receiving DC and DRG stimulation during a trial period of 16 days, patients were asked which of the 2 methods they preferred. Patients with a successful trial period with one or both stimulation methods received a fully implantable system.

Results: Twelve patients were included. After finishing the trial period, 10 patients (83.3%) preferred DRG stimulation and 2 (16.7%) preferred DC stimulation (P = 0.04).

Conclusion: To our knowledge, this is the first study to compare these 2 neurostimulation methods in patients with CRPS confined to the knee. Results show that the probability of the preference for either neurostimulation treatment significantly deviates from chance in favor of DRG stimulation.

KEYWORDS

Complex regional pain syndrome, knee, patients' preference, dorsal Column stimulation, dorsal root ganglion stimulation

INTRODUCTION

Complex Regional Pain Syndrome (CRPS), formerly known as reflex sympathetic dystrophy (RSD) or algodystrophy, is a collection of locally appearing painful conditions following a trauma. Although CRPS mainly occurs in the feet or hands, other locations are also reported (1). CRPS exceeds in both intensity and duration the expected course of the original trauma. The main clinical features are continuing pain and sensory, vasomotor, sudomotor, and motor trophic disturbances (2). CRPS is a clinical diagnosis based on signs and symptoms described in criteria sets. Currently, the use of the International Association for the Study of Pain (IASP) clinical Budapest diagnostic criteria is recommended (3). The natural history of CRPS is not always positive and can result in permanent disability.

Until now, little has been known about patients with CRPS confined to the knee. In a systematic review, we concluded that CRPS confined to the knee should be considered as a separate phenotype, distinct from CRPS of more distal locations (4). In addition, uncertainty remains regarding the best treatment for CRPS confined to the knee (4). In the Netherlands, all patients with CRPS are treated according to the Dutch Guidelines (5) (updated in 2014). However, as earlier literature shows, patients diagnosed with CRPS confined to the knee are difficult to treat (6-8).

Dorsal column (DC) stimulation is an accepted, effective and safe way of treating specific types of neuropathic chronic pain. In the Netherlands, driven by reimbursement policies, this therapy is used as a last resort for patients in whom the more conservative treatment (eg, oral pain medication) has failed. The presumed mechanism of action is based on electrical stimulation of the large ascending fibers located in the dorsal columns (A beta-fibers), which leads to inhibition of the nociceptive signal entering the spinal cord through the dorsal root (A delta- and C-fibers). CRPS is the second most common indication for DC stimulation, failed back surgery syndrome being the first (9). DC stimulation can provide evident and clinically relevant pain reduction in patients with CRPS (10-14).

The dorsal root ganglion (DRG) is a different target for neurostimulation. The DRG plays a pivotal role in the development and maintenance of chronic pain (15). The ganglion houses the cell bodies of primary sensory neurons, including those cells that transmit pain information to the central nervous system (15). In 2011, the first patients received DRG stimulation for their chronic neuropathic pain. After 12-month follow-up, patients experienced improvement in pain symptoms, health-related quality of life, and their mood (16). In a prospective case series by van Buyten et al., 8 patients with CRPS of the lower extremities received DRG stimulation after a successful trial period. Follow-up of 12 months showed improvement in quality of life in all patients and a reduction in pain ≥50% compared to baseline in 6 of the 8 patients ($P < 0.05$) (17).

Our department has experienced both the failures and successes of DC stimulation in several patients diagnosed with CRPS confined to the knee. When DRG stimulation be-

came available, 1 patient with CRPS confined to the knee was successfully treated using this method (18); this result gave rise to the present study. Based on our hypothesis that DRG stimulation would be more specific than DC stimulation, we compared both methods of neurostimulation in patients with CRPS confined to the knee.

The aim of this trial was to explore patients' preferences in treatment by neurostimulation of their chronic neuropathic-like pain due to CRPS confined to the knee.

METHODS

The institutional research ethics committee approved this study (MEC-2014-170).

Design

This was a prospective, observational, crossover, cohort study comparing 2 methods of neurostimulation, that is, DC and DRG stimulation in randomized order. All patients were diagnosed with CRPS confined to the knee according to the IASP clinical Budapest diagnostic criteria (3) and received (in randomized order) both methods of neurostimulation in succession during a trial period of 16 days in total. During this period, all patients were asked to keep a diary in which they registered their pain intensity on a visual analog scale (VAS) 3 times a day (19). After the trial period, all patients were asked to state which stimulation method they preferred as treatment. The study was registered at www.trialregister.nl (NTR5662).

Study population

Patients diagnosed with CRPS confined to the knee who visited the outpatient pain clinic were invited to participate. To be included, a patient had to meet all the following inclusion criteria: ≥1 year of CRPS confined to the knee; diagnosed according to the IASP clinical Budapest diagnostic criteria; minimum age of 18 years; no improvement in symptoms after ≥1 year of treatment according to the Dutch guidelines for CRPS (updated in 2014) (5); and a pain intensity of ≥50 mm measured on a VAS of 0 to 100 mm. Table 1 presents the inclusion/exclusion criteria.

Intervention

Neurostimulation methods are fully implantable medical devices which are placed epidurally and produce controlled electrical stimulation to spinal neural tissue. For this study, in randomized order, using a crossover design, we applied DC stimulation (Medtronic Inc.®; Fridley; MN, USA) with one 8-contact lead, and DRG stimulation (St. Jude Medical Inc.®; Little Canada; MN, USA) with two 4-contact leads.

Table 1. Inclusion and exclusion criteria for participation in the study

Inclusion criteria	Exclusion criteria
Over 1 year CRPS confined to the knee, diagnosed according to the IASP clinical Budapest diagnostic criteria	Previous neurostimulation
	Depression or anxiety disorder measured with the Hospital Anxiety and Depression Scale (HADS)
	Pregnancy, or pregnancy desire within 1 year
Minimum age 18 years	Patients unable to complete the questionnaires
No improvement of symptoms after at least 1 year of treatment according to the Dutch guidelines for CRPS in primary care	Body Mass Index > 35
	Life expectancy < 1 year
	Implantable cardioverter defibrillator, pacemaker
Pain intensity of at least 50 mm measured on a visual analog scale 0-100 mm	Anticoagulant drug therapy or disturbed coagulation
	Immunocompromised patients
	Drugs/medication/alcohol addiction

CRPS, complex regional pain syndrome; IASP, international association for the study of pain

Following patient consent and study entry, baseline measurements were made (T0). Patients used the 2 neurostimulation methods during the trial period, which lasted 16 days in total. On day 1, implantation of the stimulation leads of both methods took place. A qualified physician with extensive experience in implantation of DC and DRG stimulation systems (F.J.P.M.H.) implanted (under local anesthesia) one 8-contact lead for DC stimulation and two 4-contact leads for DRG stimulation at the same time, during the same procedure. All leads were sutured to the fascia with soft tissue anchors, and the external lead exit point was protected with a bandage.

During the first week, patients received stimulation method 1 (T1); between the 2 stimulation methods, a washout period of 2 days was included (ie, a period without any stimulation, T2); during the second week, patients received stimulation method 2 (T3). A randomization based on a computer program decided the order of stimulation. A qualified nurse took care of turning on the stimulation method, of securing the right settings (DC stimulation was set between 30 and 60 Hz), and of the evaluations during the trial period based on the patients' report and diaries.

The effect of either stimulation method was considered successful if the patient reported at least 50% reduction of pain compared to the situation just prior to that method of stimulation and/or at least a slight improvement on the global perceived effect (GPE) scale (20) after that stimulation. When one of the stimulation methods was considered successful, the patient was eligible to continue treatment with that stimulation method. In case both of the stimulation methods were considered successful, the patient was allowed to choose the stimulation method he or she preferred.

A second surgical procedure, under general anesthesia, took place on day 16 of the trial period. A qualified physician (F.J.P.M.H.) implanted an implantable pulse generator (IPG)

in the abdomen or buttock of the patient for the lasting stimulation and removed the leads of the other system. Patients then entered the long-term follow-up period of 12 months. In case both stimulation methods failed, both were explanted during the second surgical procedure. During the 12-month follow-up period, patients visited the pain department at 1, 3, 6 and 12 months after the second surgery.

Statistical analysis

The primary outcome parameter was the patient's preference for one stimulation method over the other, being a binomial variable. As this was an explorative study, the aim of the statistical analysis was primarily descriptive, not inferential. The proportion of patients preferring one stimulation method over the other will be reported, including the 95% confidence interval (CI) of that proportion (Clopper-Pearson Exact method). Analyses were performed using IBM SPSS Statistics 21 (IBM Corp. Armonk. NY, U.S.A).

RESULTS

Of the 74 patients considered for inclusion, 60 were excluded because 1) the diagnosis CRPS of the knee could no longer/not be confirmed, 2) they had already received treatment with neurostimulation, or 3) they were unwilling to participate. Of the remaining 14, 1 patient dropped out during the first operational procedure. In this patient, it proved impossible to implant the two 4-contact leads of the DRG stimulation, possibly due to degenerative deviations in the lumbar spine. Another patient dropped out during the trial period because he experienced sensory complaints in both legs the day after the first operational procedure. The sensory complaints were not objectivized by a neurologist, and an infection or epidural bleeding was ruled out. However, to reduce any potential risk of damage, the leads of both systems were removed shortly thereafter; the complaints disappeared immediately after removal and no permanent injury occurred.

This left 12 patients who finished the entire trial period: 11 females, 1 male; mean age 38.7 (range 22 to 57) years. In this group, mean VAS score at baseline was 68 on a scale of 0 to 100 (0 representing no pain, 100 representing worst imaginable pain). None of the included patients had demonstrable nerve injury in the affected knee (as measured by an electromyogram). Coverage of the painful area during implantation, was achieved in every patient with placement of the DC stimulation lead at the 8^{th}, 9^{th} or 10^{th} thoracic vertebra (Th-8, Th-9 or Th-10) and placing the DRG stimulation leads at the 3^{rd} and 4^{th} lumbar vertebrae (L-3 and L-4). Figure 1 shows the lead placement in a representative patient: the DC stimulation lead tip was positioned at Th-10 and the DRG stimulation leads were positioned at L-3 and L-4.

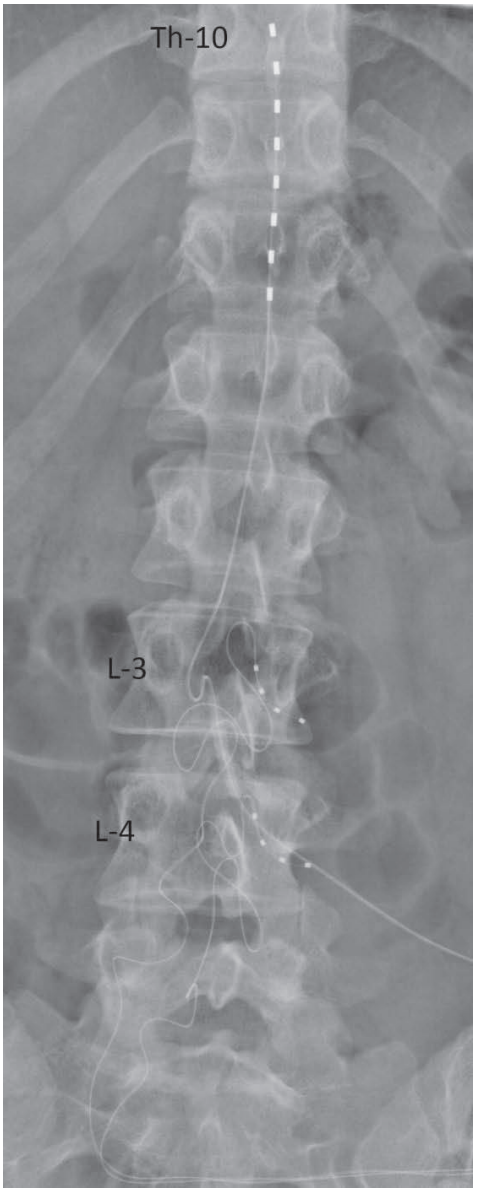

Figure 1. Lead placement during trial period
Th-10, 10th thoracic vertebra; L-3/L-4, 3rd and 4th lumbar vertebrae

Patients' Preference

Ten patients (83.3%) preferred DRG stimulation and 2 [16.7%; (95% CI: 0.02 to 0.48)] preferred DC stimulation (P = 0.04, one-sample binomial test).

In 5 patients, both stimulation methods were considered successful (patients 2, 4, 10, 11, and 13). These patients were allowed to decide which stimulation method they would have implanted permanently. Four patients (2, 4, 10 and 13) chose the DRG stimulation. Their main reason for this was that (in contrast to DC stimulation) they felt no stimulation vibrations. Moreover, during the evaluation of DC stimulation, all mentioned that they had to adjust the stimulation intensity multiple times a day. One of these patients also chose DRG stimulation because DC stimulation did not cover the whole painful area. In contrast, patient 11 chose DC stimulation because she liked the fact that she felt the stimulation vibrations and found that her walking ability had improved more with DC stimulation.

For all 12 patients, the stimulation method they preferred was implanted during the second surgical procedure.

The implanted method

In 7 of the 12 patients, the decision regarding which stimulation method was to be implanted was based on the fact that only one stimulation method proved successful after completing the trial period (patients 1, 3, 6, 7, 9, 12, and 14). The 4 patients who had success with only DRG stimulation stated that the vibrations of DC stimulation were intermittent to intensive and rather nonspecific (ie, the area covered by stimulation was larger than the painful area alone) or did not stimulate the actual painful area. The patient in whom only DC stimulation worked stated that DRG stimulation provided no pain relief, and no improvement was experienced in relative to the baseline GPE score.

Measurements during the trial

During the trial period, patients returned to our department 3 times. At each visit, the nurse turned on/off the stimulation method and made an evaluation based on the patient's self-report and diary. Mean VAS scores were calculated for each stimulation method based on the 3 scores in the patient's diary on the last day of stimulation with that method. Using the GPE scale, patients were asked at T1 and T3 to rate how much their condition had changed in comparison with T0 and T2, respectively. All patients responded that their condition had (much) improved and that they were (absolutely) satisfied with the result based on their preferred stimulation method. Table 2 presents these data.

Adverse Events

During the trial period, 3 adverse events were experienced by 2 patients; these were judged by the investigators to be related to the device or to the surgical procedures. One patient had cerebrospinal fluid leak with associated headache after the first surgical procedure; in this patient, all leads were removed during the second surgery, due to possible infection, and 3 months later, the device of choice (ie, DRG stimulation) was implanted. Another patient was admitted to hospital for a few days because of elevated temperature; however,

no active infection was demonstrated on blood tests. The patient with sensory complaints in both legs 1 day after the first procedure was excluded from the study; nevertheless, this patient was reported as experiencing an adverse event, possibly related to the device. The sensory complaints were not objectivized by a neurologist, and an infection or epidural bleeding was ruled out.

Table 2. Scores on the VAS and GPE, and patients' preference during the trial period

Patient ID no.	VAS score T0	Stimulation 1	VAS score T1	GPE T1	VAS score T2	Stimulation 2	VAS score T3	GPE T3	Patients' preference
1	82	DRG	71	No change	83	DC	32*	Much improved*	DC
2	76	DRG	10*	Much improved*	78	DC	0*	Much improved*	DRG
3	85	DC	54	Slightly improved*	70	DRG	33*	Slightly improved*	DRG
4	70	DC	0*	Completely recovered*	35	DRG	0*	Completely recovered*	DRG
6	74	DRG	49	Slightly improved*	82	DC	78	No change	DRG
7	50	DC	24*	No change	31	DRG	11*	Slightly improved*	DRG
9	70	DRG	21*	Slightly improved*	65	DC	51	Slightly improved*	DRG
10	85	DRG	36*	Slightly improved*	90	DC	51	Slightly improved*	DRG
11	71	DC	3*	Much improved*	80	DRG	16*	Much improved*	DC
12	75	DC	49	No change	46	DRG	67	Slightly improved*	DRG
13	80	DC	43	Slightly improved*	67	DRG	35	Much improved*	DRG
14	63	DC	67	No change	61	DRG	30*	Much improved*	DRG

VAS, visual analog scale; GPE, global perceived effect scale; DRG, dorsal root ganglion; DC, dorsal column.
*Trial success
T0, baseline; T1, after stimulation 1; T2, after washout period; T3, after stimulation 2

DISCUSSION

The aim of this prospective trial was to explore patients' preference in treatment by neurostimulation of their chronic neuropathic-like pain due to CRPS confined to the knee. In a crossover design, DC stimulation was compared with DRG stimulation. The results show that, in these patients, the probability of the preference for either neurostimulation treatment significantly deviates from chance in favor of DRG stimulation.

DC vs. DRG stimulation

Reduction in pain due to DC or DRG stimulation turned out to be comparable between the patients, as shown in table 2. So, apparently, patients have other, probably individual, reasons to prefer a stimulation method, and this is not solely based on obtained pain

relief. This finding is in line with the results found by others (21). DC stimulation is known to be somewhat nonspecific and to have more positional side-effects (22). In this study, both these items were often mentioned by patients as reasons for their preference for DRG stimulation over DC stimulation. Three patients stated that DC stimulation did not cover the entire painful area. In contrast, 4 patients reported that DC stimulation covered an area that was actually larger than their painful area. During evaluation of DC stimulation, 6 patients said that they thought the stimulation vibrations were too strong, even after lowering the intensity themselves. They also mentioned they found it bothersome to have to adjust the stimulation level several times a day, as well as experiencing different stimulation intensities during walking, sitting, or lying down. Therefore, the present study confirms that DC stimulation can be rather nonspecific and has more positional side effects. None of these limitations were mentioned in relation to DRG stimulation and were reasons for patients to prefer that form of stimulation.

In one patient, it was impossible to implant the DRG leads, whereas the DC stimulation lead was placed in the right position without any problem. A computerized axial tomographic scan showed a degenerative lumbar spine, but no neuroforaminal stenosis. Thus, even when the neuroforamina appear to have a normal entry, it can be difficult to place DRG leads, in our case possibly due to degeneration of the lumbar spine. This can be an important item when considering the feasibility of applying DRG stimulation. Also, in 2 of the patients, motor stimulation occurred when stimulating one of the DRG leads. Adjusting the settings turned out to be the solution to remove the motor stimulation. This motor stimulation did not occur with DC stimulation.

Methodological Remarks

The trial period included a washout period of 2 days; there are no earlier reports concerning the appropriate duration of a washout period. At T2 (after the washout period), all patients reported that the pain relief ceased within minutes to hours after stopping the first stimulation method; this applied to both DC and DRG stimulation. However, when comparing the T0 VAS scores with the T2 VAS scores, different VAS scores emerged in 7 of the 12 patients. This could imply that patients need a longer recovery time to prevent a carryover effect or that a response shift occurred during the first stimulation. As the VAS scores were compared before the start of a stimulation method and at the end of that specific stimulation method, the ascertainment of success cannot have been influenced by (events in) the washout period.

Regarding adverse events, as 2 different stimulation methods were implanted simultaneously, it was impossible to relate these events to either stimulation method. Of the 2 patients with a possible infection, in one patient this necessitated removal of all the leads during the second surgical procedure. No wound complications were seen in the patient

group. As infection and wound complications are reported with either neurostimulation treatment (23), this did not differ in the present patient group.

All surgical procedures were performed by the same qualified physician (F.J.P.M.H.). The first surgical procedure was undoubtedly intense for patients, because 2 different stimulation methods were implanted simultaneously. Patients later reported that especially placement of the 2 DRG leads was more painful than placement of the single DC lead, which always took place first during the procedure. Also, for the physician, these procedures took longer, implying a potentially higher risk of infection and/or contamination (24).

A possible limitation of the present study was the lack of blinding; future studies should aim to find a more controlled, blinded way of comparing the 2 neurostimulation methods using a crossover design. Monitoring patients' preference of stimulation method only immediately after the trial period can also be considered as a limitation of the present study. After all, patients can change their mind over time. So the results at trial end cannot be generalized to the long term.

CONCLUSION

To our knowledge, this is the first study to explore preferences for DC or DRG stimulation in patients with CRPS confined to the knee. The results show a preference for DRG stimulation over DC stimulation, because DRG stimulation can be more specific for the painful area and is independent of the body position, and patients appreciated the absence of stimulation vibrations. It is not possible to generalize the results of this study to other CRPS locations (the foot or the hand). Nevertheless, we recommend that physicians consider DRG stimulation, rather than DC stimulation, in case of intractable CRPS confined to the knee. Follow-up data from this study are currently being processed.

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