Therapeutic value of spinal cord stimulation in irritable bowel syndrome – a randomized cross-over pilot study

Running head: Spinal stimulation for IBS

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Abbreviations:

IBS: Irritable bowel syndrome
IBS-C Constipation-dominant irritable bowel syndrome
IBS-D Diarrhea-dominant irritable bowel syndrome
IBS-M Mixed-type irritable bowel syndrome
SCS: Spinal cord stimulation
VAS: Visual analogue scale
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Abstract (250 words)

Irritable bowel syndrome (IBS) is characterized by abdominal pain and changed bowel habits. Spinal cord stimulation (SCS) has been used for treatment of chronic pain syndromes. Animal studies have shown SCS to reduce the reaction to colonic balloon distension, known to be increased in IBS patients. To elucidate the potential for SCS as treatment for IBS, a pilot study was performed. Ten IBS patients (age 26-56 years) were recruited. A SCS system with a 4-polar electrode was implanted at the T5-T8 level. After a two-week run-in, a randomized, crossover design SCS during 6 weeks was compared to no stimulation, with an ensuing stimulation period for 12 weeks; total study period 28 weeks. Patients recorded pain level, pain attacks, diarrheas and global quality of life in a diary. At end of the study patients could choose to retain their SCS system or have it removed. Nine patients completed the whole trial. During stimulation periods the median pain scores were significantly reduced from VAS 7 (4-8) to 3 (2.5-7) and to 4 (2-6) during early and late stimulation periods, respectively (p<0.03-0.04). Pain attacks were numerically reduced. A few patients reported reduced number of diarrheas. After study termination, six patients chose to retain their SCS system. To conclude, SCS is a minimally invasive treatment option for pain in IBS. With SCS the pain level was reduced though with merely a trend for number of attacks and diarrheas. The efficacy of SCS in IBS pain indicates a possible usefulness in other painful bowel disorders.

Keywords: Spinal cord stimulation; irritable bowel syndrome; abdominal pain; diarrhea
Introduction

Irritable bowel syndrome (IBS) is characterized by chronic recurrent abdominal pain or discomfort concurrent with altered bowel habits as described by the Rome III criteria (2). The cause of IBS is considered to be multifactorial. Stressful life events commonly precede the onset of IBS symptoms (31). As well, the risk of developing IBS during the first year after gastroenteritis is tenfold higher than for the general population (30).

Patients with IBS seem to have an altered intestinal motility and sensitivity. Balloon distension of the distal colon in patients with IBS causes pain at considerably lower inflation volumes than in controls (29). IBS patients also have lower thresholds for perception and discomfort to distension in the rectum as well as in the esophagus (33) indicating a generally increased visceral sensitivity. Furthermore, in IBS a low-grade inflammation in the gut mucosa, with an increase of mast cells, has been observed (24). Numerous treatment options are available for IBS but show suboptimal clinical results (8). A search for new therapeutic strategies and treatment modalities is thus warranted.

Spinal cord stimulation (SCS) has evolved to a useful, cost-efficient, minimally invasive and reversible therapy for different forms of chronic pain. Controlled trials suggest effectiveness of SCS for pain in the complex regional pain syndrome, lumbosacral rhizopathy, limb ischemia and angina pectoris (22). Application of SCS is usually perceived by the patient as paresthesiae or a “tingling sensation”, as a precondition for a pain-relieving effect, since the electrode has to be positioned so that resulting paresthesiae cover the painful region. Using a remote control the patients can turn stimulation on and off at their own discretion. An SCS-system and illustrative X-ray image are shown in Fig 1.
The physiological mechanisms underlying the pain-relieving effect of SCS are only partially understood (9, 21). In a series of studies SCS was applied in rats subjected to colorectal distension (10). Data shows that the visceromotor response to distension was substantially diminished by SCS. Sensitization of the rat colon with acetic acid markedly enhanced the response to balloon distension. This reaction was completely normalized by SCS (10). Similarly, after trinitrobenzenesulfonic acid-induced colonic hypersensitivity, SCS was found to be significantly effective in order to ameliorate symptoms when applied one month later when the mucosa showed no signs of inflammation (11). Based on these data, Krames and Moussad (19) reported the case of a patient with treatment refractory IBS-D in whom a quadripolar electrode was implanted at the upper level of the T8 vertebral body. On stimulation, both pain and the number of diarrheal episodes were reduced. Apart from IBS, case series of abdominal pain (chronic pancreatitis and pain secondary to abdominal surgery) have shown to be effectively treated with SCS (13, 16, 18). The combination of animal data and the successful trial in a single patient inspired us to conduct a controlled clinical pilot study. The fact that effective SCS necessarily produces sensations precludes blinded trials; instead a randomized crossover design using on-off periods was employed to minimize placebo responses.

The primary aim of our study was to investigate if the typical abdominal pain of IBS was ameliorated by SCS. Secondary aims were to evaluate effects of SCS on diarrhea or constipation, quality of life (QoL), and side effects, as well as tolerability to SCS as validated by the patient’s preference to keep the stimulation equipment after the study period. The investigation was carried out as an exploratory investigation with a limited entry of ten selected subjects.

**Materials and Methods**
Patients

Eligible patients were selected from a database. Inclusion criteria were age 18-60 years of age, fulfillment of the Rome III criteria (2), episodic abdominal pain exceeding 4 on a 0-10 VAS scale (12) and stable symptoms for the past 2 years. A thorough clinical work-up was done, including routine blood, endocrine and electrolyte status, hepatic enzyme screening and lactose tolerance test, tissue transglutaminase serology as well as colonoscopy or barium enema. Patients with significant somatic (fibromyalgia, urinary tract or gynecological symptoms, neurological disease) and psychiatric co-morbidity were excluded. None of the included patients took any medication as this treatment had previously failed. Patients were given both oral and written information about the study. Eligible patients were then referred to the implanting neurosurgeon for further information about the implantation process. The selected patient’s mean age was 29.7 (range 18-46) years; seven women and three men, six of which with diarrhea-predominant (IBS-D) subtype of IBS with >3 loose bowel movements a day, and four of the mixed subtype (IBS-M) with inter-changing bowel habits of constipation and diarrhea. Written consent after full information was obtained from each participant. The study was approved by the regional Ethics committee of Stockholm, Sweden (04-674/3).

Study design

A quadripolar SCS-lead (Quad-plus®, Medtronic Inc., Minneapolis, MN, USA) was implanted via a percutaneous puncture at the T11-T12 level of the dorsal epidural space in local anesthesia with the patient in prone position. The electrode was advanced to the mid-thoracic level, aiming for a final tip position around T6-T8, and intraoperative stimulation yielded paresthesiae covering the abdomen (with or without paresthesiae in the legs). The electrode was connected to an impulse generator (Itrel-3®, Medtronic Inc.) implanted subcutaneously in the upper left quadrant of the abdomen. In search on the ideal implantation level and stimulation parameters we used the patients report of paresthesiae over the lower
abdomen as a successful implantation. The stimulation frequency was set at 50 Hz with other parameters (electrode pole combinations, pulse amplitude 1.3-3.3 mA and pulse width 0.24-0.45 ms) set to produce adequate paresthesiae covering the usual region of pain with comfortable intensity. Suitable parameters were selected and set shortly after implantation when the patient was mobilized. Stimulation was thereafter turned off. During the subsequent on-going trial reprogramming of the stimulation parameters was allowed if necessary to uphold optimal stimulation. Randomization was done by envelope draw by independent person immediately after surgical electrode implantation.

According to the study protocol, stimulation was not permitted during the first two weeks after surgery as a run-in period. Thereafter, patients were randomized by envelope draw to either of two programming schedules: one starting with SCS for a six weeks period (early start) (A), and another with the initial six weeks without SCS (delayed start) (B) (Fig. 2). During the stimulation-ON periods patients were requested to use SCS for at least 8-12 h at an intensity yielding comfortable paresthesiae. If pain attacks appeared, patients were encouraged to increase the stimulation intensity until relief was achieved. After six weeks, patients without stimulation were crossed-over to stimulation and vice versa. After another six weeks both programs included continued stimulation for an additional 12 weeks up to a total study period of 26 weeks including the run-in period. After a consecutive two-week period without stimulation the trial was terminated. During the whole study period patients recorded in a daily diary: 1) number of pain attacks, 2) number of diarrhea episodes, 3) average pain level for the day and 4) assessment of average QoL. For the latter two items patients were instructed to use a numeric 0-10 VAS.

Patients were scheduled for outpatient visits, at weeks 2, 8, 14, 26 and 28 after the implantation. Patient compliance was monitored, since the impulse generator stores
information on the percentage of elapsed time with SCS stimulation-ON. At termination of
the study, participants were offered to keep the implanted SCS system or have it removed.
All patients underwent a structured follow-up telephone interview between 18 to 78 months
after study termination. At the telephone interview a questionnaire was used to assess their
present pain level, medication, use of SCS, side effects and global satisfaction. Patients were
also asked whether they would have participated if they had known the outcome in advance,
and if they would recommend SCS treatment to someone else with similar gastrointestinal
problems.
All patients were evaluated with the hospital anxiety and depression scale (HADS) (36) and a
modified version of the gastrointestinal symptom rating scale for IBS (GSRS-IBS) (34).

Statistics
Statistical processing was performed utilizing GraphPad Prism 6 (GraphPad Software Inc.,
San Diego, CA, USA) employing the Friedman ANOVA multiple comparisons test for the
pre-stimulation period versus the early and late stimulation periods. Analyses where made for
responders to treatment, as well as for all stimulation periods as a full analysis set (FAS).
Wilcoxon matched-pairs test was used for individual comparisons. Spearman correlation
analysis was used to evaluate correlations between pain intensity, the number of pain attacks
and diarrhea episodes. All parameters are expressed as medians with 25-75 percentiles and
range.

Results
Out of a total number of 63 eligible patients, 18 were selected by the gastroenterologist and
referred to the neurosurgery team for more specific information about the procedure. Ten of
these volunteered to participate in the study according to the protocol (Fig. 2 and 3). All
patients had a GSRS-IBS scoring between 3 to 5 for different domains before onset of the study. The HADS score was below 7 in 6 patients, whereas increased anxiety was found in two patients and depression in one. The final position of uppermost pole of the electrode is given in table 1. One patient chose to leave the study after ten weeks for undisclosed reasons. The remaining nine patients completed the entire study. Six of those reported a satisfactory result with stimulation, whereas three did not. The three patients without benefits from stimulation also chose to have their SCS-system removed after study close-out. The remaining six have continued their stimulation treatment beyond the trial period, with the longest follow-up 6½ years.

_Pain intensity, pain attacks, diarrhea and quality of life_

On comparison, the median pain intensity scores, number of pain attacks and number of diarrhea episodes were lower during the early and late stimulation periods than during the prestimulation period and non-stimulation periods (Fig. 4). This difference was statistically significant for pain intensity throughout all groups (p<0.04), for both the early (p<0.03) and late (p<0.04) (cf. Fig. 4) stimulation periods, but failed to reach statistical significance for number of pain attacks and diarrhea. When limiting the analysis to pain intensity responders (as described in post-hoc experience), this difference became even more evident with a reduction of pain intensity by 25.5% and 25.7% for the early and late stimulation periods as compared to the prestimulation period.

In figure 5 graphs illustrating the effects of SCS on pain intensity, number of pain attacks and diarrheas over time are shown. In analysis of the FAS (including data from all cases, see statistics above), the stimulation effect on pain intensity decreased progressively over the early six-week stimulation period, and then again during the late 12-week stimulation period reaching significance for the whole group (p<0.05), specifically for weeks 15-20 and 21-26 of the stimulation period versus the prestimulation period (p<0.05). The number of pain attacks
showed a similar pattern with numerical reductions during the SCS period; significantly reduced by weeks 15-20 and 21-26 as compared to the prestimulation period (p<0.04) (Fig. 5). Conversely, pain intensity and number of pain attacks all showed a divergent pattern during stimulation-ON and stimulation-OFF periods. The diarrhea frequency displayed a different pattern that was neither related to pain intensity nor to the number of pain attacks. There was no difference in effects on the pain whether the stimulation-OFF period occurred prior to stimulation period or vice versa.

Correlations

Figure 6 shows the overall correlation between the pain intensity and the number of pain attacks (r=0.52, p<0.0001). Before SCS there was only a borderline significant correlation (r=0.64, p<0.07), whereas during the stimulation-OFF periods the correlation became markedly significant (r=0.64, p<0.003) also occurring during the stimulation-ON periods (r=0.43, p<0.003). This indicates an association between the rated pain intensity and number of pain attacks. However, there was no correlation between the IBS pain intensity or number of pain attacks versus number of diarrhea episodes (r=0.21 and r=0.19, respectively), possibly indicating separate mechanisms behind these symptoms. Furthermore, after SCS there was only a weak trend for an increased QoL. At onset of stimulation QoL was estimated to VAS 4.9 ±0.8, whereas at 6 weeks QoL was 5.5 ±1.1 and at the end of the study 6.5 ±0.5 using a linear estimate displaying a trend for improvement.

The HADS showed elevated values for anxiety in three patients and depression in one of ten patients, yielding no relationship to the response to SCS.

Post-hoc experience
Compliance to the study protocol appeared to be excellent in all patients. During periods without stimulation the pulse generator was set to 0 and the patient was unable to use the SCS. During the stimulation periods the stimulators were turned “on” for an average of 60% of study time and no pulse generator showed a usage below 41% indicating that no patient used the stimulator less than 8 hours per day. When limiting analysis to pain intensity responders, the effect of SCS became evident with a reduction of pain intensity by 53 ±10.6 (range 18-95)% for the summarized early and late stimulation periods as compared to the maximum pain scoring during the prestimulation period.

Reprogramming to uphold adequate paresthesia coverage of the painful area during the trial was necessary for four patients, two of whom required a second reprogramming (a routine in SCS therapy to ascertain adequate paresthesiae).

Six patients reported side effects during the trial or at follow-up. Two patients reported a feeling of tiredness during stimulation periods. Another two patients reported sensations of unsteady gait during stimulation probably related to paresthesiae in the legs (cf. 22). One patient reported uncomfortably high intensity stimulation in her legs, pain at the implantation site of the stimulator and transient headache upon removal of the SCS system.

Follow-up

After study close-out six patients opted to keep their SCS systems. At follow-up after on average 61 months, three patients who opted to keep the SCS system reported that their SCS was still in use. Two patients experienced over the first four years progressively less pain with stimulation therapy, even to an extent that they ceased to use the SCS on a regular basis. However, both patients have chosen to retain the equipment, should the symptoms return in the future. In one patient both pain and diarrheas were eradicated and no longer present.

Another patient had her SCS system removed because of safety concerns in conjunction with
an MRI examination at three years from implantation. No early or late complications were associated with the implantation.

**Discussion**

The approach of our study was to prospectively evaluate SCS applied for IBS pain, with a randomized crossover trial design. Blinding was not possible to accomplish, as paresthesiae are always sensed during SCS. A statistically significant reduction of perceived pain intensity was observed during the stimulation periods. Data also showed a progressively increasing pain relief over prolonged study time. In addition, not only pain intensity but also the number of pain attacks per day decreased with SCS. There was a trend that SCS had a positive effect also on other IBS symptoms, but failed to reach statistical significance for the number of pain attacks and diarrheal episodes per day. This result is possibly related to the small number of patients included in the study and the fact that we did not specifically include patients with IBS-D, but rather patients with a more common IBS profile with pain as the principal IBS symptom. However, correlation analysis showed a markedly significant relationship between pain intensity and number of pain attacks, whereas pain intensity as well as pain attacks and diarrheal episodes did not. It is therefore likely that similar mechanisms are involved in pain intensity and pain attacks, while diarrhea stems from another source.

A majority of our patients apparently benefited from the treatment as witnessed by their choice to retain the SCS system after the trial. As the battery is depleted after about 5 years and the stimulator eventually ceases to function, our patients have had their stimulators exchanged, at their own request. The fact that this procedure will demand repeat surgery clearly supports that patients found the treatment beneficial. Taken together, six patients had benefit from the SCS treatment whereas three did not. This could be extrapolated to a
responder rate of 60-70%, which is in fact comparable to the outcome of SCS when applied for neuropathic pain (22). However, IBS pain cannot be directly compared neuropathic pain because the IBS pain is more multi-faceted with numerous underlying possible pathological mechanisms, many of which are unlikely to respond to SCS. It should be noted that the common success rate of IBS patients when studied in clinical trials is 30-40% at its best (8). The average pain reduction in our SCS study was found to be in the range of 25% which is low as compared to standards for analgesic drugs claiming at least a 30% pain reduction as a clinically important difference (4). The pain reduction also seemed surprisingly low as compared to the patients’ spontaneous comments on the exceptional treatment effect. This disparity between the pain experience and pain sensation may be due to the linear monitoring of pain sensations by VAS, and the meaningfulness of a pain relief that patients may experience. Furthermore, as no wash-out period was interspersed between the stimulation-ON and stimulation-OFF periods a carry-over effect from the stimulation-ON period cannot be ignored which may have reduced the therapeutic gain of SCS. As verified by post-hoc experience a meaningful pain relief was still achieved in the majority of our IBS patients. Therefore, it appears that the success rate of the SCS treatment could be more advantageous as an adjunct in the management of IBS in selected patients.

Abdominal pain was the only symptom significantly reduced by SCS in all subcategories with IBS. As for diarrhea frequency, only two of the five fully participating IBS-D patients experienced a clear reduction of diarrhea with stimulation. Nonetheless, our results suggest that adjunct symptoms of bowel dysfunction such as diarrhea and constipation are less responsive to SCS than IBS pain per se.
It is not clear in which way that SCS influences the gut-brain axis. Krames and Foreman have hypothesized that the effect is mediated via the spinothalamic tract and the visceral pain-mediating postsynaptic tract deep in the dorsal columns (20). Furthermore, antidromic activation of sensory nerves innervating the gut may be of importance, as shown in other SCS experiments (20). In animal studies Qin et al. has shown SCS to influence the transmission of visceroreceptor information in the spinal cord (26, 27). Qin et al. also performed extracellular microrecordings of dorsal horn neurons in the rat L6-S2 spinal segments. These neurons responded to colorectal distension and could be inhibited by SCS (27).

The first investigations of SCS for gastrointestinal effects were done by Pescatori et al. (25) who studied colonic motility in two patients with neurological disease (multiple sclerosis, spina bifida) and severe constipation. Both patients received SCS at the T8-9 level similar to our stimulation level. During stimulation the authors found that the patients’ bowel movements were regularized which is different from our experience.

Occasional gastrointestinal effects of SCS as applied for other indications have been reported as adverse effects (17, 32). In these studies SCS was not used intentionally for gastrointestinal effects and the electrodes were implanted remotely from the gut. Successful SCS treatment of abdominal pain in mesenteric ischemia has also been documented (1). The electrode was located at the T6 level and stimulation induced paresthesiae in the abdominal area. The patient was reported to be relieved still after one year. Presently, there are several publications of studies on SCS applied for different kinds of abdominal pain with at least 70 patients reported as successfully treated (14-16). It is worth noting that these successful treatments were achieved after careful patient selection and prior temporary trial stimulation. For IBS specifically, two additional case reports, have recently been published confirming that SCS may have beneficial effects in this condition (6, 7). A different type of neurostimulation,
selective stimulation of sacral nerves, has also been tried against IBS pain. Reports show a significant reduction of IBS-related symptoms and improved QoL in highly selected IBS patients but with no detectable small bowel motility effect (6, 7) as well as rectal wall relaxation and highly significant reduction of symptoms in IBS-D and IBS-M (5).

The presence of paresthesiae on stimulation has been considered a prerequisite for an optimal SCS effect and this precludes blinded designs of clinical SCS trials. Nonetheless, a few studies with stimulation intensities below the threshold for paresthesiae have been performed with SCS in angina pectoris and neuropathic pain (3, 35), usually demonstrating a clear effect of SCS at subparesthetic intensity, but that a somewhat higher stimulation intensity providing paresthesia is more effective. In our study, one patient chose to stimulate with low intensity and reported a satisfactory effect also with stimulation subthreshold to paresthesiae, but was urged to continue with paresthetic stimulation, as intended with the study protocol.

In conclusion, our study suggests that SCS may be an optional treatment modality for IBS pain. It appears that the principal beneficial effect of SCS is amelioration of the IBS-related pain. There is a trend for other symptoms of IBS to be positively influenced. However, these effects have to be further explored in more extensive studies. The high prevalence of IBS motivates larger randomized studies to establish the possible long-term usefulness of SCS in the management of this disorder and its cost-benefits.

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Disclosures

Medtronic Inc., Minneapolis, MN, USA, supported the trial with all the implant materials, but had no impact on the study design, analysis or interpretation of the results. The authors G.L., J.W., B.L. or P.M.H. have no competing financial or other interests to report.
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Legends to tables and figures

Table 1. Summary of patient data including demographics, IBS subtype, level of the uppermost electrode pole, group randomization, retained spinal cord stimulation system and medical history.

Figure 1. Spinal cord stimulation system. Anterior-posterior X-ray image of electrode position in a patient (#9).

Figure 2. Flowchart of clinical trial outline, with stimulation-ON and stimulation-OFF periods indicated. Randomization was performed immediately after implant.

Figure 3. Flowchart of the study protocol. Group A started with spinal cord stimulation upon onset of the study period. Group B had delayed start by six weeks until cross-over. The diagram also shows the number of patients available for each step.

Figure 4. Box-and-whiskers diagram showing the median, 25-75 percentiles and range for pain intensity (top), pain attacks per day (middle) and diarrhea (bottom) during the prestimulation, early and late spinal cord stimulation periods for all responders (n=6) to treatment. Significant differences were obtained for pain intensity during both the early and late stimulation periods, but not for pain attacks and diarrhea.

Figure 5. Box-and-whiskers diagram showing the median, 25-75 percentiles and range for pain intensity (top), pain attacks per day (middle) and diarrhea (bottom) during the whole study period for all included patients (n=9). There was no difference in pain effects whether the stimulation-OFF period occurred prior to stimulation-ON period or vice versa.

Figure 6. Correlations between pain intensity and pain attacks per day during the prestimulation period. Each data point represents daily pain scoring versus number of pain
attacks during that day. There was a trend for a co-variation between pain intensity and number of daily pain attacks during the prestimulation period. During the stimulation-ON period and the stimulation-OFF periods correlations were statistically significant.
Table 1. Demographics implantation and spinal cord stimulation parameters of study patients.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at IBS debut</th>
<th>IBS subtype</th>
<th>Age at implant</th>
<th>SCS parameters</th>
<th>Level of highest electrode pole</th>
<th>Study group</th>
<th>Opted to keep SCS</th>
<th>Medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>35</td>
<td>IBS-M</td>
<td>39</td>
<td>Contacts: 0 -, 2 +. Pw: 390 µs A: 3.5 V</td>
<td>T7/8</td>
<td>B</td>
<td>Y</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td>F</td>
<td>26</td>
<td>IBS-D</td>
<td>31</td>
<td>Contacts: 0 &amp; 3 -, 1 +. Pw: 450 µs A: 8.0 V</td>
<td>T7</td>
<td>B</td>
<td>N</td>
<td>Dystrophia myotonica</td>
</tr>
<tr>
<td>M</td>
<td>18</td>
<td>IBS-D</td>
<td>25</td>
<td>Contacts: 2 -, case +. Pw: 270 µs A: 3.5 V</td>
<td>T7/8</td>
<td>A</td>
<td>N</td>
<td>Asthma</td>
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<tr>
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<td>T7</td>
<td>A</td>
<td>Y</td>
<td>Previous transverse colon tumor, Dukes A</td>
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<tr>
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<td>Contacts: 3 -, case +. Pw: 330 µs A: 7.5 V</td>
<td>T7</td>
<td>B</td>
<td>N</td>
<td>No clinically significant</td>
</tr>
</tbody>
</table>

IBS, irritable bowel syndrome; SCS, spinal cord stimulation; Pw, pulse width; A, ampli
Figure 2.

A.

- Stim >8-12 h/d
- "Prestim" → "Early stim" → "No stim" → "Late stim" → "Poststim"

B.

- Stim >8-12 h/d
- "Prestim" → "No stim" → "Early stim" → "Late stim" → "Poststim"

Stimulation period
Period without stimulation

Implant

0 2 8 14 26 28 weeks
2 weeks 6 weeks 6 weeks 12 weeks 2 weeks
Figure 3.

Assessed for eligibility (n=63)

- Excluded (n=53)
  - Not meeting inclusion criteria (n=42)
  - Declined to participate (n=8)
  - Other reasons (n=3)

Randomized (n=10)

Allocated to group A (n=5)
  - Received allocated intervention (n=5)
  - Did not receive allocated intervention (n=0)

Allocated to group B (n=5)
  - Received allocated intervention (n=4)
  - Did not receive allocated intervention (withdrew participation) (n=1)

Lost to follow-up (n=0)
  - Discontinued intervention (n=0)

Analyzed (n=5)
  - Excluded from analysis (n=0)

Lost to follow-up (n=0)
  - Discontinued intervention (n=0)

Analyzed (n=4)
  - Excluded from analysis (n=0)
Pain attacks (no. per day)

Pain intensity (VAS)

- Pre-stim period
- No stim period
- Stim period