Reduced Areas of Spontaneous Neuropathic Pain After Spinal Cord Stimulation Treatment

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Objectives: Spinal cord stimulation (SCS) is known to be an effective treatment for a range of neuropathic pain (NeP) conditions, although further clinical evidence is required. Clinical observations suggest that 1 aspect of the treatment effect is a reduction in the area with spontaneous NeP. The aim of this study was to quantify the areas of spontaneous NeP in SCS patients and to correlate these with changes in pain intensity and quality of life.

Methods: Twenty-six SCS patients with NeP rated their pain intensity on a numerical rating scale (0 to 10) and completed the SF-36 health survey. In addition, their areas of spontaneous pain were photographically documented before and during SCS treatment, and the areas were transferred to phantom drawings and digitally quantified.

Results: Areas of spontaneous NeP were reduced by 62% (interquartile range, −15 to 78). Pain intensity was reduced from 7.5 ± 1.1 before to 4.9 ± 1.7 during treatment (mean ± SD) and most domains of the SF-36 health survey also improved with SCS treatment. Using linear regression, no correlation was found between relative reduction in areas of spontaneous NeP and relative reduction in pain intensity as well as in absolute improvement in quality of life assessed by SF-36. A correlation was found between improvement in pain intensity and in quality of life.

Discussion: The results indicate that the main impact of SCS on the patients’ quality of life is not the reduction of the painful areas, but rather the reduced pain intensity in the remaining area.

Key Words: neumodulation, spinal cord stimulation, NeP, neurological examination

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pineal cord stimulation (SCS) is a minimally invasive surgical treatment for chronic neuropathic pain (NeP), originally described by Shealy et al in 1967.1 It is used to treat a range of conditions such as pain due to failed back surgery syndrome,2,3 angina pectoris,4,5 diabetic neuropathy,6 peripheral vascular disease,7,8 complex regional pain syndrome (CRPS),9,10 and peripheral nerve damage.11

The theoretical foundation behind the therapy was originally based on Melzack and Wall’s Gate Control Theory,12 but it has become evident that the mechanism of action is likely to be a complex interplay of many factors. Changes in the spinal neurotransmitter GABA/glutamate balance13,14 and acetylcholine release,15,16 an antidromically mediated reduction of spinal neuronal hyperexcitability,17 recruitment of a spinal-brainstem-spinal loop,18,19 and cerebral modulating mechanisms20–22 are some of the potential mechanisms that may play a role for the effect of SCS. Despite the expanding experimental knowledge of how SCS may exert its effect, there is still a need for additional data on the clinical efficacy.

The success rate of the treatment varies depending on the underlying etiology of pain. In most studies of SCS outcome, the primary success parameter is the patient-reported reduction in perceived pain; also, improvement in other outcome measures such as quality of life, physical function, work status, and consumption of analgesics has been reported in numerous studies.2,3,6,10 The active SCS treatment evokes a feeling of paresthesia in the treated area. It has been hypothesized that these paresthesias could affect the processing of sensory information from the periphery, but findings from studies using quantitative sensory testing have not clearly demonstrated such an effect.23,24

Many patients with chronic NeP have areas of spontaneous NeP that tend to increase in size over time (as is often the case in painful diabetic neuropathy) or extend well beyond the area of pain that can be attributed to the original trauma that triggered the painful condition (as is often the case in CRPS or pain after peripheral nerve injury). We have made the clinical observation that the areas of the body affected by spontaneous NeP seem to diminish in patients treated with SCS. If this is the case, a reduction in the areas of spontaneous NeP could represent a potential new clinical outcome parameter.

We therefore decided to investigate the changes in areas of spontaneous NeP after SCS treatment. To the best of our knowledge, this has not been examined before. We hypothesized that a possible reduction in areas would correlate with reduced pain intensity and improved quality of life. A method for quantifying the areas of pain is described.

PATIENTS AND METHODS

Patients

Between September 2008 and February 2012, 90 NeP patients were implanted with SCS at the Department of Neurosurgery, Aarhus University Hospital, Denmark.
All patients accepted for SCS treatment had a history and symptoms clearly indicating that their pain was of neurogenic origin. In case of doubt, patients were examined by an experienced specialist in NeP (T.S.J.). As a part of the follow-up for treatment effect, patients rated their pain intensity and quality of life before and at regular intervals after the implantation. In addition, their areas of spontaneous NeP were photographically documented. Patients were eligible for the present study if all of the following inclusion criteria were fulfilled: (1) SCS treatment for at least 3 months, (2) reported pain reduction during treatment, (3) patient-completed questionnaires about pain intensity and quality of life, and (4) photographic documentation of areas of spontaneous NeP of a sufficient quality to allow an accurate display of areas of pain from all relevant angles.

Assessment of Pain Intensity and Quality of Life
Postal questionnaires were used for ratings of pain intensity and quality of life before and during SCS treatment. Pain intensity was recorded for 7 consecutive days on a 0 to 10 numerical rating scale (NRS) with 0 being no pain and 10 being the worst pain imaginable. Quality of life was described using a standard SF-36 questionnaire, a well-validated tool for evaluating health-related quality of life. The questionnaire is divided into 8 domains, 4 of which relate primarily to physical well-being and 4 primarily to mental well-being. For correlations between changes in the areas of spontaneous NeP and pain intensity and quality of life, data were used from NRS and SF-36 scores obtained either at the same time or as close as possible to the time of area documentation.

Photographic Documentation
The areas of spontaneous NeP were documented before SCS implantation and at one of the outpatient visits at the hospital after the implantation. Patients were asked to delineate their areas of spontaneous NeP, and the examiner (K.M. or B.M.C.) used a pen to outline the areas directly on the patient’s body according to his/her instructions. Areas were documented with a digital camera.

Area Estimations
An anterior-posterior outline drawing of the whole body supplemented with lateral projections of the legs was used to create a set of drawn phantoms, scaled to size A3 (297 × 420 mm), to present each body part. Each patient was assigned the phantom drawing set that enabled the most accurate representation of the distribution of pain. All photo sets were then anonymized and assigned a random number generated by an automated generator (http://randomizer.org). An investigator (M.E.M.) without knowledge of the patients or the photo sets then examined each set and transferred the areas of pain to the matched phantom drawings (Fig. 1). Painful areas outlined in the drawings were then manually digitized by the same examiner using a pen tablet (Intuos2; Wacom, Kizo-shi, Japan) and converted to centimeters² using image analyzing software (Quantify One; KLONK, Slagelse, Denmark).

Data Analysis
Data were analyzed using Stata IC 11.0 (StataCorp LP, TX). The relative reduction in the areas of spontaneous NeP was calculated as \[1 - \left(\frac{\text{area}_{\text{beforeSCS}}}{\text{area}_{\text{afterSCS}}}\right)\]. From the 7-day pain registration, a mean was calculated and the relative reduction was calculated as \[1 - \left(\frac{\text{NRS}_{\text{beforeSCS}}}{\text{NRS}_{\text{afterSCS}}}\right)\]. Changes in scores for each SF-36 domain were calculated as absolute differences (score_{afterSCS} − score_{beforeSCS}).

The paired datasets were checked for normal distribution with the Shapiro–Wilk test (level of significance \(P < 0.05\)) and Q-Q plots. Normally distributed data are presented as mean ± SD, and compared using the Student t test. Otherwise data are presented as median [interquartile range (IQR)], and compared using the Wilcoxon signed-rank test.

The relative change in area of spontaneous NeP and the absolute changes in the 8 domains of the SF-36 were analyzed as a function of the relative change in pain intensity. The absolute changes in the SF-36 domains were analyzed as a function of the relative change of spontaneous NeP. Possible correlations were analyzed using linear regression. For all statistical tests, the level of significance was set at \(P < 0.05\).

RESULTS
Twenty-six patients fulfilled all inclusion criteria. The remaining patients either had insufficient treatment effect, incomplete questionnaires, missing or insufficient photographic documentation, or were lost to follow-up. Median age was 53 years (IQR, 43 to 64); 16 were male, 10 were female. Seven had radiating or lumbar pain after spine surgery, 7 had pain related to diabetic neuropathy, 6 had CRPS, 3 had pain after peripheral nerve injury, 2 had pain after plexus injury, and 1 had pain after root avulsion. Areas of spontaneous NeP were found in both upper and lower extremities as well on the trunk. Seven patients had unilateral pain, 19 had bilateral pain. Patients with bilateral pain had both of their painful areas analyzed.

Median duration of SCS treatment at photographic follow-up was 32.5 weeks (IQR, 24 to 48). Median time to completion of questionnaires about pain intensity and quality of life was 27 weeks (IQR, 22 to 48).

All patients were implanted with a percutaneous lead placed in the epidural space by an experienced implantor (K.M. or J.C.S.); the equipment was standard SCS implants manufactured by St Jude Medical, St Paul, MN. Before the implantation, all patients were in a stable pharmacological pain treatment optimized or approved by a specialist in pain medicine (L.N. or T.S.J.).

Area Analysis
Median reduction in areas of spontaneous NeP was 62% (IQR, −15 to 78). The change was statistically significant (\(P = 0.005\)).

Pain Intensity and SF-36
Mean pain intensity before SCS surgery was 7.5 ± 1.1 and at follow-up 4.9 ± 1.7, a mean reduction of 36% ± 21% (statistically significant, \(P < 0.0000\)) (Fig. 2). Comparisons of SF-36 scores before and after SCS treatment showed statistically significant improvement for all domains except general health (Table 1).

Correlations
Linear regression analysis showed no correlation between relative change in areas of spontaneous NeP and relative change in pain intensity. Correlation coefficient: 1.48 (CI, −1.11; 4.08), \(P = 0.248\).

Analysis of the correlation between relative change in areas of spontaneous NeP and absolute change in SF-36
domains showed no statistical significance either (Table 2). Analysis of the correlation between absolute changes in SF-36 domains and relative change in pain intensity showed statistical significance for vitality, mental health, and bodily pain.

DISCUSSION

Patients included in this study experienced significant pain relief and reported improvement in most domains of SF-36. It is to be noted this study was not aimed at documenting SCS treatment efficacy, but at investigating the changes in the areas affected by spontaneous NeP, and the significance of those changes.

There was a reduction in the areas of spontaneous NeP. An analysis of the correlation between reduction in pain intensity and improvements in quality of life expressed as an increase in SF-36 scores showed a direct correlation for most domains. In contrast, no correlation was seen between the reduction in the area of spontaneous NeP and the reduction in pain intensity or improvements in SF-36 domains. Taken together, these findings suggest that areas of spontaneous NeP do not represent an outcome parameter of clinical implications for pain intensity or quality of life in chronic pain patients in SCS therapy.

We did not assess the patients for areas of allodynia or hyperalgesia. The examined patients had a wide range of NeP conditions, and some (notably the diabetic neuropathy patients) did not have allodynia or hyperalgesia. Patients with painful diabetic neuropathy usually complain of deep aching pain but rarely have hyperalgesia or allodynia, which otherwise is a classical symptom of NeP. Spontaneous (nonevoked) pain is the symptom common to all the patients in the study, and it is the symptom that our patients in general list as the most debilitating symptom affecting their quality of life. In this study we therefore chose to concentrate on spontaneous NeP.

It is important to note that the present study is open and based on a limited number of patients. The patients had different chronic pain conditions, and there was some variation in the interval from SCS implantation to follow-up. Larger populations would allow stratification of patients by diagnosis or treatment duration.

Area Assessment

A key element in the analysis of outcome is the validity of the estimation of the areas affected by spontaneous NeP. Pain drawings were first introduced by Palmer in 1949, and after their subsequent re-introduction by Melzack in 1975.
1975 as part of the McGill Pain Questionnaire, they have been an integral part of pain assessment. A few studies have linked psychosocial factors and pain severity with the size of painful areas; less work has been done investigating changes in pain drawings as an outcome after an intervention.

A study examining 51 patients over varying periods of time (mean 71 d between completion of 2 sets of pain drawings) showed that the areas remained constant over time. This, however, does not exclude that the lack of correlation between the reduction in pain areas and in pain intensity is an expression of a different time course of the therapeutic efficacy either related to different mechanisms or to a different sensitivity of 2 parameters of the same control mechanism.

Pain drawings are subject to different sources of error including bias. For example, pain drawings may be completed by patients in ways that were not intended by investigators despite careful instructions. In this study the pain mapping was done by an investigator who examined the patients directly. The subsequent quantification is subject to observer bias. We tried to minimize this by having another examiner transfer the marked areas to phantom drawings. For the quantification of the resulting pain drawings, a commonly described method is manually correlating areas to a template drawing with separation of the body in a number of regions. In the present study, we measured the areas outlined on the phantom drawings directly using a software program, a method shown to be reliable in a recent Danish study. We believe this approach led to a more accurate quantification of the outlined areas.

An unresolved issue is the challenge posed by converting a 3-dimensional (3D) area to a 2-dimensional drawing. A recently described computer system using a 3D model for pain assessment might be a step toward a future solution to the problem. Nevertheless, we believe the method described in this paper does represent a reliable estimate of the area of pain in patients.

Areas of Spontaneous Neuropathic Pain

Provided the area estimations reliably reflect the patients’ areas of spontaneous NeP, our data suggest that unlike a reduction in pain intensity, a reduction in the areas of pain does not seem to be linked with an improvement in the patients’ quality of life. A previous study suggested a strong positive correlation between pain intensity and area of pain in chronic pain patients. However, the results presented here may reflect that in the case of SCS, the main impact on the patients’ quality of life is not the reduction in painful areas, but rather the intensity of pain in the remaining area.

It is of interest to note that in other studies where the area of allodynia and intensity of spontaneous pain have been compared in NeP, no correlation (similar to the present study) was found between these parameters after pharmacological interventions such as gabapentin. Although it is unclear what the area of pain reflects, it may be linked to the size of neurons involved in processing nocuous information. The lack of correlation suggests that pain intensity and area of pain are not mediated by the same mechanisms.

CONCLUSIONS

In this open study we demonstrated a significant reduction in the areas of spontaneous NeP in patients treated with SCS. Pain intensity was significantly reduced, and most domains of the SF-36 health survey improved with treatment. There was no significant correlation

<table>
<thead>
<tr>
<th>SF-36</th>
<th>Pain (NRS)</th>
<th>Physical Function</th>
<th>General Health</th>
<th>Vitality</th>
<th>Mental Health</th>
<th>Role Physical</th>
<th>Role Emotional</th>
<th>Social Function</th>
<th>Bodily Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before SCS implantation</td>
<td>7.5 ± 1.1</td>
<td>44 ± 27</td>
<td>45 ± 22</td>
<td>27 ± 21</td>
<td>51 ± 20</td>
<td>0 (0-25)</td>
<td>0 (0-67)</td>
<td>48 ± 32</td>
<td>21 ± 16</td>
</tr>
<tr>
<td>At follow-up</td>
<td>4.9 ± 1.7</td>
<td>51 ± 26</td>
<td>43 ± 18</td>
<td>40 ± 24</td>
<td>66 ± 19</td>
<td>12.5 (0-75)</td>
<td>67 (0-100)</td>
<td>63 ± 30</td>
<td>40 ± 15</td>
</tr>
<tr>
<td><em>P</em></td>
<td>0.0000</td>
<td>0.0696</td>
<td>0.6392</td>
<td>0.0105</td>
<td>0.0009</td>
<td>0.0266</td>
<td>0.0047</td>
<td>0.0159</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Values shown as mean ± SD for variables fitting the normal distribution, median (interquartile range) is used for nonparametric data.
NRS indicates numerical rating scale; SCS, spinal cord stimulation; SF-36, Short-Form 36.
between the reduction in areas of spontaneous NeP and reduced pain intensity, or improvement in SF-36 domains. Areas of spontaneous NeP do not seem to represent an important clinical outcome measure for treatment success.

ACKNOWLEDGMENTS

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REFERENCES


### TABLE 2. Correlation Between Changes in SF-36 Data, Pain Intensity, and Areas of Spontaneous Pain

<table>
<thead>
<tr>
<th>SF-36 Absolute change (0-100)</th>
<th>Pain Intensity</th>
<th>Areas of Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation</td>
<td>P</td>
</tr>
<tr>
<td>Physical function</td>
<td>0.09 [−0.27; 0.46]</td>
<td>0.616</td>
</tr>
<tr>
<td>General health</td>
<td>0.27 [−0.05; 0.58]</td>
<td>0.094</td>
</tr>
<tr>
<td>Vitality</td>
<td>0.57 [0.17; 0.99]</td>
<td>0.008</td>
</tr>
<tr>
<td>Mental health</td>
<td>0.51 [0.16; 0.85]</td>
<td>0.006</td>
</tr>
<tr>
<td>Role physical</td>
<td>0.33 [−0.48; 1.14]</td>
<td>0.409</td>
</tr>
<tr>
<td>Role emotional</td>
<td>0.19 [−0.65; 1.03]</td>
<td>0.641</td>
</tr>
<tr>
<td>Social function</td>
<td>0.44 [−0.13; 1.01]</td>
<td>0.122</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>0.45 [0.18; 0.73]</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Linear regression analyses of correlation between absolute changes in the 8 domains of SF-36, and relative changes in pain intensity or in areas of spontaneous pain. P-values marked with bold for statistically significant correlations. SF-36 indicates Short-Form 36.


