Case Report

An N-of-1 Trial as an Aid to Decision-Making Prior to Implanting a Permanent Spinal Cord Stimulator

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ABSTRACT

Objective. Limited evidence supports the efficacy of spinal cord stimulation (SCS). Therefore, it is crucial to assess the usefulness of this invasive procedure before implanting permanent electrodes in each patient. An N-of-1 trial is an experiment in which a single participant undergoes periods of comparative treatments. We illustrate how an N-of-1 trial design may permit clinicians to conduct such an assessment in an individual patient.

Design. Case report.

Setting. University teaching hospital.

Patients. A 61-year-old man patient with refractory postherpetic neuralgia scheduled for SCS implantation.

Interventions. Percutaneous octapolar lead placement into the epidural space for SCS at T5-T6, and placement of transcutaneous electrical nerve stimulator (TENS) electrodes upon the painful area on the patient’s back. We provided electrical stimulation via TENS or SCS according to a computer-generated random number list. Each stimulation period lasted 5 hours, followed by 1 hour of rest.

Outcome Measures. At the end of each period, a blinded assessor evaluated the degree of pain relief, pain intensity, area of stimulation, and the patient’s satisfaction. The study had a 5-day duration.

Results. In this patient, spinal stimulation was equally efficacious as TENS.

Conclusions. We encourage clinicians to perform an N-of-1 trial in every patient before implanting permanent electrodes for SCS.

Key Words. N-of-1 Trial; Spinal Cord Stimulation; Efficacy

Introduction

A 61-year-old man patient had a 23-month history of postherpetic neuralgia that affected T3 through T6 on the right. The patient had both constant pain of moderate/severe intensity, often burning, as well as one to three episodes of paroxysmal severe pain about every 6 hours despite medical treatment, the pain affected all dimen-
sions of health-related quality of life. For example, tactile allodynia in the back and front of his chest prevented him from wearing a shirt.

Previous treatments consisted of sympathetic blocks and the use of anticonvulsants (carbamazepine, gabapentin), tricyclic antidepressants (desipramine, amitriptyline, imipramine), strong opioids (oxycodone and methadone), and multiple combinations of these medications without success. Because of the lack of response, we considered the patient to be a potential candidate for spinal cord stimulation (SCS).

Spinal neurostimulation delivers low-voltage electrical stimulation to the spinal cord, which is thought to provide analgesia by activating nociceptive inhibitory systems [1], and increasing levels of gamma-aminobutyric acid and adenosine in the dorsal horn [2] which reduce neuronal hyperexcitability. It is increasingly used for treatment of refractory pain, including postherpetic neuralgia [3]. However, its efficacy has not yet been defined [4].

A recent systematic review of the literature identified limited evidence in favor of SCS for chronic pain [5]. Two small randomized controlled trials were found: one compared spinal stimulation vs physical therapy in patients with complex regional pain syndrome [6] and the other compared spinal stimulation with surgery in patients with failed back syndrome [7]. Both studies showed that spinal stimulation was superior in terms of pain relief or satisfaction. The small number of subjects enrolled in these two trials (54 and 50) and the lack of functional improvement in any of the trials are shortcomings that limit the applicability of the findings. As the patient had not yet had a trial of a transcutaneous electrical nerve stimulator (TENS) unit, we felt it would be possible to compare both modalities in a randomized N-of-1 trial to help determine whether SCS would be likely to benefit. We therefore secured written, informed consent from the patient to conduct an N-of-1 randomized double-blind trial of SCS vs a TENS unit.

Methods

An N-of-1 trial is an experiment in which a single participant undergoes pairs of treatment periods; one period involves the use of an experimental treatment (in this case, SCS) and the other involves the use of an alternate (in this case, TENS) or placebo therapy. Treatment periods are replicated until the clinician and patient are convinced that the treatments are definitely different or definitely not different [8] or a prespecified number of paired treatment trials is reached.

We chose TENS as a comparator because TENS is a therapeutic modality that produces sensations which allow maintenance of masking both for the patient and physician.

We estimated that 10 pairs of trials would be needed to detect a statistically significant difference between the SCS and TENS. We followed the same procedure as that for the calculation of sample size in crossover studies. We assumed that the probability of having pain relief with SCS was 0.6 and with TENS was 0.3, and that the probability of having pain relief with both treatments was 0.3 (phi = 0.53). We set the alpha error to 0.1 and the beta error to 0.2. We did not plan to stop the evaluation early.

We asked the patient to document pain intensity on a pain questionnaire every 6 hours for 5 days prior to implantation of the spinal electrode. We placed the latter percutaneously under local anesthesia, and with fluoroscopic guidance. An octapolar lead (Medtronic model 3898-61 Octad®, Medtronic, Minneapolis, MN) was advanced into the epidural space at T5-T6, and the tip was placed at T3. We desired a stimulation pattern that covered the patient’s area of pain as completely as possible. We achieved this initially with an amplitude of 3.0 V, a pulse width of 200 µseconds, and a rate of 120 Hz. The lead was tunneled approximately 12 cm and secured at the point of exit. We confirmed the position of the lead with fluoroscopy (see Figure 1 for X-ray). In addition, we placed two TENS electrodes on the skin within the painful area of the back of the

Figure 1 A-P X-ray view of the spinal electrode.
patient. The initial TENS (STIM-T) parameters of stimulation were identical to the SCS. Six hours later, we started the trial.

Both the SCS and TENS controls were placed in the same opaque fabric bag that was secured with tape to maintain blinding. A physician not involved in the patient’s clinical care or assessment opened the bag and turned on one or another device according to a computer-generated random number list (STATA 8.0 SE). Each stimulation period lasted 5 hours, followed by 1 hour of rest. At the end of each stimulation period, a blinded assessor evaluated the degree of pain relief, using a five-point Likert scale (from worsening of the pain to complete pain relief); pain intensity, using a 0–10 numerical rating scale (0 = no pain; 10 = the worst imaginable pain); highest and lowest pain intensity in the past 5 hours; the area stimulated; and the patient’s satisfaction with the result of that stimulation session. The study had a 5-day duration and was conducted around the clock. Afterwards, the patient had three more days of unblinded assessment.

To optimize pain relief and ensure that the area of the paresthesia covered the previously painful area, every 24 hours the polarity, amplitude, pulse width, and rate of the stimulus of SCS and TENS unit were modified, based on the information collected the previous day. The patient’s medication regimen remained unchanged during the duration of the study: methadone, doxepin, carbamazepine, and gabapentin.

To assess meaningful pain relief (defined as at least moderate pain relief on the Likert scale), we estimated the number of pairs of trials in which the patient reported meaningful pain relief or being satisfied with the SCS and not with TENS, and calculated $P$ values using the exact McNemar test. For the analysis of pain intensity, we calculated the means for pain intensity, lowest and highest pain intensity, and for the number of episodes of paroxysmal pain during each type of treatment in all trials. To detect differences between the treatments, we used paired $t$-tests with nine degrees of freedom (number of pairs of trials—1).

<table>
<thead>
<tr>
<th>Table 1 Percentage of trials in each time period</th>
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<tbody>
<tr>
<td>Treatment</td>
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<tr>
<td>SCS</td>
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<td>TENS</td>
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SCS = spinal cord stimulation; TENS = transcutaneous electrical nerve stimulator.

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<th>Table 2 Numbers of pairs of trials in which the patient reported adequate or inadequate pain relief and satisfaction by treatment (total number of pairs of treatments = 10)</th>
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<tr>
<td>Spinal Cordstimulation Adequate Pain Relief</td>
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<tr>
<td>Adequate pain relief</td>
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<tr>
<td>Inadequate pain relief</td>
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<tr>
<td>TENS Satisfied</td>
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<tr>
<td>Not satisfied</td>
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* Exact McNemar test.

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<th>Table 3 Pain intensity levels using the numerical rating scale (0–10) by type of treatment</th>
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<td>Outcome</td>
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<td>Mean pain intensity ± SD</td>
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<tr>
<td>Mean number of paroxysmal pain episodes ± SD</td>
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<tr>
<td>Mean maximum pain intensity ± SD</td>
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<td>Mean minimum pain intensity ± SD</td>
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TENS = transcutaneous electrical nerve stimulator.

Results

Mean pain (±SD) intensity in the 5 days prior to the study was 5.4 ± 2.7; the mean number of paroxysmal episodes of pain per 6 hours during the five pretrial days was 1.16 ± 1.24 (range: 0–4) and the mean peak pain intensity was 6.3 ± 2.7.

The patient completed all of the 10 scheduled pairs of trials. In 70% of the trials during both treatments, the patient reported that the area of paresthesia coincided with the painful area. Seventy percent of the SCS trials were performed during the late afternoon or overnight. The distribution of the treatments across time is displayed in Table 1.

Pain relief was similar during both treatments; in two paired treatments, the patient obtained pain relief with SCS and not TENS, and in one pair of treatments the patient achieved pain relief with the TENS and not SCS (Table 2). The degree of satisfaction was also similar with TENS and SCS (Table 2).

Pain intensity, number of episodes of paroxysmal pain, maximum and minimum pain intensity were also similar with the TENS and SCS (Table 3).
Discussion

This case illustrates how an N-of-1 trial may allow clinicians to assess in a single subject whether to proceed with planned permanent electrode placement for SCS. In our patient, spinal stimulation produced a similar degree of pain relief and a similar decrease in pain intensity as TENS and therefore we did not proceed to permanent electrodes and receiver implantation.

Prior efforts to evaluate the effectiveness of temporary SCS electrodes have been reported [9], but they have not rigorously followed an N-of-1 experimental paradigm. N-of-1 analgesic trials with different treatment comparators, washout periods, or outcomes can be designed to accommodate clinicians’ needs. We based the calculation of the number of trials needed on the proportion of times a subject would have pain relief with SCS, TENS, or with both treatments. We could have based it on the difference in pain intensity. For instance, to detect a difference of 1.5 units on a scale from 0 to 10 between TENS and SCS with a standard deviation for the difference in pain intensity of 1.2, and alpha error of 5% and a beta error of 20%, seven trials would have been sufficient. A longer washout period could have been used or even desirable as the duration of pain relief may outlast the period of stimulation. These are few examples that illustrate other ways in which N-of-1 trials could be designed and conducted. Nonetheless, when conducting an N-of-1 trial, the treatment allocation should be randomized and efforts made to assure double-blind evaluations during [10].

An N-of-1 trial is superior to the traditional assessment of temporary leads as it controls for the patient's and the evaluator's expectations and the placebo effect. The decrease in pain intensity that this patient exhibited with both treatments emphasizes the need for such evaluation before concluding that the patient is responding to spinal stimulation. This evaluation is of course in addition to the medical and behavioral assessments that patients scheduled for invasive pain therapies should undergo to ensure that these therapies are used in those patients who are most likely to benefit [11].

We have demonstrated that the extra complexity involved in running an N-of-1 trial is not substantial. Similarly, we want to show that the extra costs that might be associated with an N-of-1 trial should not deter clinicians from performing these trials. First, the marginal cost of conducting an N-of-1 trial is low because customary care in the screening phase before permanent implantation also requires close monitoring. In our case, the incremental expense was limited to the cost of only the additional days the patient remained in the hospital. Second, we are obliged to assess the efficacy of the invasive and costly procedures we perform. Lastly, the incremental benefit of N-of-1 trials could extend beyond the benefit of a sole individual if the information from these trials is recorded by pain clinics. This information will create a structure to support performing a meta-analysis of trials accumulated from individual N-of-1 trials [12] across pain clinics to obtain an estimate of treatment effectiveness across a broader population of pain sufferers.

We encourage clinicians to perform an N-of-1 trial in every patient before implanting permanent spinal electrodes given the limited data supporting their efficacy.

References

