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Blinded Efficacy Testing of High Frequency Spinal Cord Stimulation

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Abstract

Objective: Traditional spinal cord stimulation (SCS) relies on paresthesias to mask patients' pain perception. This restricts the high-quality evaluation of SCS's efficacy. 10-kHz high-frequency (HF10) therapy, however, is a paresthesia-free modality of SCS. As such, the introduction of this technology creates the opportunity to evaluate SCS's efficacy with appropriate patient and provider blinding to treatment. We report a case of a patient with axial low back pain who, without her knowledge, underwent "blinded" testing of the device by her spouse.

Case: A 66 year-old female with four years of axial low back pain and a diagnosis of post-laminectomy syndrome presented for consultation after failing multiple medical and surgical treatments. HF10 SCS trial provided her with greater than 50% pain relief with reduction in her opioid consumption. As such, decision was made to pursue permanent implantation. Without her knowledge, the patient underwent 'blinded' testing of the devise's efficacy by her spouse who repeatedly inactivated (and subsequently activated) the stimulator while she slept.

Discussion: This is the first report to evaluate the efficacy of HF10 in treating chronic axial low back pain where the patient was truly blinded to the SCS treatment (i.e., she did not know if the device was on or off). Future studies can lead to appropriately blinded randomized control studies to generate high-level evidence for HF10's efficacy and harm in a variety of pain condition.

Keywords: Spinal cord stimulation; Post-laminectomy syndrome; Chronic pain

Introduction

The first documented use of spinal cord stimulation (SCS) dates to 1967 when the American neurosurgeon C Norman Shealy described the subdural placement of an electrode to treat intractable pain in a 70 year-old patient suffering from a bronchial carcinoma [1]. Over the last fifty years as the technology has improved and supporting outcome data accrued, SCS has gained increased acceptance for the treatment of a variety of chronic pain conditions. SCS is currently approved by the FDA for chronic pain of the trunk and limbs, intractable low back pain, leg pain, and pain from post-laminectomy syndrome. In Europe, it has additional approval for refractory angina pectoris and peripheral limb ischemia. Despite the empirical evidence for efficacy, the mechanism(s) through which SCS alters pain perception is unclear. While the primary site of action of SCS is local, there are multiple structures that may be affected including the dorsal root ganglia (DRG), central processes of peripheral sensory fibers, cells of the dorsal horn (second order sensory neurons, interneurons, glia), and white matter tracks both ascending and descending. Other proposed mechanisms of action include the release of inhibitory neurotransmitters within the dorsal horn including serotonin, acetylcholine and γ-aminobutyric acid (GABA), and inhibition of nociceptive conduction through the activation of large A-fibers [2]. Clearly, for a subset of patients a placebo effect is likely active, particularly given the fact that SCS represents a relatively high degree of invasiveness [3].

Traditional low-frequency SCS delivers pulse frequencies (typically around 50 Hz) with the goal of creating paresthesias overlapping with the patient's pain distribution to mask pain perception [4]. Given tradiational SCS's dependency on inducing paresthesias, it is difficult to blind patients and investigators to treatment; this is a major limitation for design of clinical trials for which efficacy is a primary outcome measure. In October 2015 the first randomized, controlled trial comparing traditional SCS with high frequency SCS at 10 kHz (HF10) for the treatment of chronic back and leg pain was published [4], and HF10 therapy was approved by the FDA in April 2016. Notably, HF10 therapy does not rely on the induction of paresthesias to mask pain, nor does HF10 induce any sensation in the patient, for that matter. Instead, HF10 has been empirically shown to decrease pain via delivery of high frequency pulses centered at the T8-T11 spinal region [5]. Given this "paresthesia-free" technique, the prior limitation of blinding study subjects and investigators to treatment is obviated. However, to our knowledge no randomized control trial with blinding to treatment designed to evaluate efficacy of HF10 therapy has been published. In this report, we present a case of a patient who underwent permanent implantation of the HF10 SCS device and underwent 'blinded' testing of devise efficacy by her spouse who without her knowledge repeatedly inactivated (and subsequently activated) the stimulator while she slept.

Case Presentation

Approval was obtained from the patient for publication of this report. A 66 year-old female presented to our clinic with four years of chronic axial and radicular low back pain in 2012. Her past medical history was significant for migraines, fibromyalgia, chronic opioid use and asthma. Her past surgical history was significant for lumbar spondylosis status post L4-5 decompressive laminectomy and fusion with no relief of her axial or radicular back pain. Subsequently, she underwent an L2-S1 decompression and fusion in 2015 with improvement in her radicular pain, but continued to have residual axial back pain located to her bilateral lower back. The pain was burning in quality. Exacerbating

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factors included standing and ambulating for any period of time. The pain was alleviated by lying supine. Prior to her laminectomy, she had undergone various interventional pain procedures including lumbar epidural steroid injections, lumbar medial branch blocks, and lumbar medial branch radiofrequency ablations with no long lasting relief. At the time of presentation her medical regimen included oxycodone ER 40 mg BID, oxycodone 10 mg q6h PRN, gabapentin 600 mg QID, alprazolam 1 mg TID, carisoprodol 350 mg QID, and duloxetine 60 mg QD.

Based on her clinical presentation and surgical history, the patient was deemed an appropriate candidate for SCS therapy. As such, after a pain psychology evaluation, the patient underwent percutaneous SCS trial lead implantation with the Nevro HF10 system in March 2016. The trial was conducted for seven days with 50% reduction in her axial back pain. The patient was also able to start tapering down her opioids during the trial. In May 2016 she underwent permanent Nevro HF10 implantation with the tip of one lead threaded to the top of the T8 vertebral body and the second lead threaded to the top of the T9 vertebral body. Of note, the patient was completely weaned off opioids within two months post-permanent SCS implantation and within four months was only taking ibuprofen for bilateral knee pain.

Upon follow up in September 2016, the patient reported overall 70% reduction in her chronic axial back pain. Interestingly, she stated that one day she woke up in the morning with significant return of her chronic burning axial low back pain. On further questioning, it became apparent that the patient's husband, without her knowledge, had decreased the energy on her stimulator the prior night while the patient was asleep. The patient then endured significant pain during the day until going to sleep that evening. While asleep, her husband then increased the energy back to its therapeutic level and the patient woke up the following morning feeling better again with roughly 70% pain reduction. She was utterly unaware of the changes her husband had performed both nights while she was asleep. Per the husband's report, after he decreased the energy level on the first night, the patient had complained of pain about twelve hours later in the late morning. The patient's husband repeated this "experiment" two other times for a total of three "trials." He admits to wanting to evaluate any possible placebo response to her SCS.

Discussion

Various neurobiological (i.e., opioid release) and psychological (i.e., enhancing expectancy) studies have described potential mechanisms for placebo analgesia [3]. As such, it is reasonable to assume that in a subset of patients SCS will generate a placebo effect with regard to pain control. Technical limitations – i.e., generation of paresthesias - restrict the high quality evaluation (i.e., generating Level 1 or 2 evidence) of efficacy of low frequency SCS technology. With the introduction of high frequency SCS, this technical limitation affecting trial design is absent. Namely, although patients will still require hardware implantation, the lack of dependency on paresthesias to mask pain relief permits appropriate blinding of patients and investigators to treatment.

In this case report, we describe a patient whose high frequency SCS was turned down without her knowledge by her spouse three times over the course of four weeks. Each time the device was turned down while she was asleep with subsequent increase in her axial back pain roughly twelve hours later upon her awakening. Her pain was then reduced significantly when her husband reactivated her SCS to its therapeutic level while she was asleep the subsequent evening, again without her knowledge of this reactivation.

While this does not eliminate the hypothesis that placebo analgesia could be contributing to patients' significant pain relief from SCS, it does demonstrate that placebo analgesia cannot entirely explain this technology's efficacy and that there must be physiologic and neurobiological mechanisms behind high frequency SCS's mechanism of action—indeed ample research has tried to elucidate these mechanisms of action in detail [2].

Conclusion

This case report serves as a brief introduction to various research paradigms that can be created in the future to further examine to what extent, if any at all, placebo analgesia plays a role in pain relief from high frequency SCS technology. Future well-designed HF10 SCS randomized control studies can be appropriately blinded and thus provide high-level evidence regarding efficacy and harm for a variety of indications. These studies also have the potential – in conjunction with a variety of technologies such as functional imaging – to provide insight into the mechanisms through which spinal cord stimulation controls pain.

Conflict of Interest Statement

Authors have no conflict of interest to disclose.

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None.

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