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Review Article

High Frequency Spinal Cord Stimulation: a Review and Introduction to a Novel Wireless Technology for Neuromodulation -

Laura Tyler. P*

Stimwave Technologies, Inc. 901 Las Olas Blvd, Suite 201, Fort Lauderdale, FL 33301, USA

***Address for Correspondence:** Laura Tyler Perryman, Stimwave technologies, 1310 Park Central Blvd South, Pompano Beach, Florida, 33064, USA, Tel: +800-965-5134; E-mail: Laura@stimwave.com

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ABSTRACT

Spinal Cord Stimulation (SCS) is established as standard of care in the management of chronic intractable back pain and leg pain. The conventional SCS frequency has certain limitations in yielding a satisfactory analgesia especially in cases of axial back pain and also due to unpalatable paresthesia resulting from the stimulation. Continued experimental work provided information about the improved results when the frequency of SCS is increased. Pilot studies and recent randomized controlled trial revealed that SCS at Higher Frequency (HF) produces better pain relief without the accompanying paresthesia. HF SCS in its current available form has an apparatus that requires implantation of all its components (electrodes, extension wires and implantable power generator) and inherits the associated complications. Our technology has introduced wireless neuromodulation where-in, and receiver to make only the electrode array needs to be inside the body and power source has wider range of stimulation parameters available, controlled by a remote device. This was approved by FDA and CE and has been in clinical use. Wireless HF stimulation in our experience with 37 cases of refractory back pain, produced the desired pain control and yet devoid of the complications related to the conventional SCS. Because of its simplicity, the device is cosmetically better with reduced surgery costs and maintenance. Further larger multicenter prospective randomized trials are expected to establish the safety and efficacy of this minimally invasive wireless technology.

Keywords: Spinal cord stimulation; Frequency; Wireless; Minimally invasive; Neuromodulation

INTRODUCTION

Spinal Cord Stimulation (SCS) is a commonly recommended procedure to treat several pain syndromes and the goals include pain relief, reduced disability and improved function. Literature supports SCS [1-4]. Studies evaluated SCS in the management of FBSS establishing its safety and efficacy including costs [2,5,6]. At the same time, the limitations and complications due to procedure as well as the technology, amounting to 40% also were reported [7,8]. Device and surgery related issues like lead migration, fracture, hardware malfunction/disconnection, Implanted Power Generator (IPG) failure, wound pain, infection indicate revision procedures [7,9,10]. In some long standing SCS patients there was tolerance and demand for increased stimulation [11-13]. Also, SCS in its conventional form fails. It has poor or low pain control in midline areas like low back, pelvis, buttocks and foot [14]. Sometimes, the incomplete coverage is due to postural changes altering the position of leads in the epidural compartment [15,16]. Some patients perceive unacceptable paresthesias over the areas of pain [17]. Technological improvements of the SCS apparatus, undoubtedly resulted in better outcomes, but all these systems use identical parameters that failed to yield sustainable axial pain relief [18]. These drawbacks have necessitated investigation of new targets and stimulation parameters viz. Dorsal Root Ganglion (DRG), High Frequency (HF). HF (1 - 10 KHz) stimulation has frequency well above the firing rates supported by most neurons and has the advantages that include absence of uncomfortable paresthesias and wider coverage of pain relief. Initial studies in 2013 were equivocal [19,20]. A systematic study regarding kilohertz frequency stimulation and chronic pain was reported by Shechter et al in experimental set up [21]. They compared the effects of 1 and 50 Hz dorsal column stimulation at high- and low intensities on conduction properties of afferent Aα/β-fibers and spinal wide-dynamic–range neuronal excitability in rats after L5 spinal nerve ligation.

Frequency and SCS

In peripheral vascular disease models of SCS, 500 Hz resulted in better vasodilatation compared to 50 Hz stimulation [22]. Transcutaneous electrical nerve stimulation in rat models, at 100 Hz also produced greater pain inhibition than lower frequencies did [23,24]. Higher frequency SCS has not been systematically evaluated for its analgesic efficiency though it has been used to control torticollis [25]. According to gate control theory, stimulated large A-fibers activate the inhibitory interneurons in the dorsal horn and thus attenuate the spinal pain transmission [26] and by increasing the frequency additional A-fibers might be recruited since KHz level stimulation provides more electrical pulses of the same intensity and duration compared to a conventional 50 Hz SCS. Also, different frequencies might be eliciting different distinct patterns of activities, such as those seen with TENS and electro-acupuncture [27,28].

SCS frequency and pain control

Shechter et al in their remarkable experiments have systematically examined the different analgesic actions produced by increased frequency SCS [21] wherein, the KHz levels of stimulation in L5 spinal nerve ligation rat model of neuropathic pain relieved the mechanical hypersensitivity. KHz SCS not only acts early with greater extent but sustained its pain inhibition effects suggesting cumulative action, a finding earlier reported in nerve injury models [29]. Schechter et al observed that HF SCS had comparable effects of pain relief, as reported with TENS and electro-acupuncture [27,30,31]. A possible correlation between duration of pain alleviation and stimulation intensity may exist and various paradigms may be tested for effective treatment even in other neuropathic syndromes [32,33]. SCS at low or high frequency induced pain inhibition that always correlated with intensity, even subthreshold levels [34]. An important message from all these models has been that neither of these frequencies even at the highest intensity could produce complete reversal of the neuropathic hypersensitivity and there were refractory instances to SCS at all frequencies and intensities [21,32,35].

SCS frequency and pain inhibition

HF stimulation blocks the conduction of action potentials and it is directly proportional to the number of activated fibers [36,37]. SCS also changes properties of afferent conduction and HF leads to conduction failure at the branch points blocking afferent signals reaching the nociceptive pathways of the spinal cord [38]. Mechanical hypersensitivity elicits abnormal activity in the myelinated afferent fibers (Aβ-fibers) of the dorsal column and inhibition of these A-fiber inputs results in inhibition of the nociceptive signals [39,40]. Traditional frequency SCS induces analgesia by activating the A-fibers of the dorsal column, but not all afferent inputs, which can be achieved by higher frequency/intensity stimulation at the DRG or the dorsal root entry zone in both small (rats) and large (goats) animals [41]. Although paresthesia elicited by SCS may not necessarily relate to the pain-relieving effect, a basic principle for conventional SCS is to create paresthesia, presumably by activating myelinated afferent fibers in the dorsal column, which overlap the affected pain region. As the

fundamental biological basis for conventional SCS-induced analgesia, the gate-control theory postulates that some of these afferent sensory neurons send collateral branches to the affected spinal segments, and activities of these large fibers drive onto inhibitory dorsal horn interneurons to inhibit spinal pain transmission [26,42]. With a fixed pulse width and duration KHz frequency SCS delivers much more electrical pulses than traditional 50 Hz and greater neuronal inhibition and accordingly greater activation of pain inhibition [43]. As a result, compared to pre and sham stimulation, 1KHz and 10KHz significantly reduced mechanical hypersensitivity in SNL rats [21]. Shechter et al proposed unique modulation of neural pathways by KHz stimulation in the form of dorsal column activation with a stochastic and asynchronous manner that probably differs from the lower frequency stimulation affecting a synchronous firing of neurons [44-46]. Higher frequency stimulation might induce changes in afferent conduction properties in peripheral as well as spinal segments and gene expressions involved in neural plasticity, different from pain suppression due to lower frequency stimulation [21]. Cuellar et al observed that HF inhibited the sensory neurons rather than activating them and thus has therapeutic advantage to induce analgesia without producing sensory phenomena like paresthesias. Thus HF stimulation was also proposed to replace conventional frequency SCS for effective pain management [41].

Clinical trials with HF SCS

A 5-center prospective multicenter pilot study was conducted on 24 patients with chronic back pain using HF SCS that had proprietary waveform and stimulation parameters from Nevro Corporation (Menlo Park, CA, USA). The four day percutaneous trial stimulation (HF following conventional SCS) demonstrated analgesia without paresthesia and 88% patients preferred HF over conventional SCS [47]. In a larger European study Van Buy ten et al had more than 50% analgesia without paresthesias in 74% of their patients implanted with HF SCS [19] as did other groups [48]. The Senza (Nevro Corp, Menlo park, CA, USA) HF10 SCS underwent a series of clinical trials and a recent randomized control trial in 198 patients with back and leg pain. The study has demonstrated long lasting (12-month) efficacy in significant number of patients [3]. HF SCS was not associated with paresthesia.

Stimwave High Frequency wireless neuromodulation

Stimwave (Stimwave Technologies Incorporated, Pompano Beach Florida 33064, USA) has introduced a miniature implant design with wireless operational capabilities of stimulation parameters. This novel minimally invasive technology has been approved by FDA and CE for clinical use to relieve chronic back pain and leg pain via SCS, peripheral nerve stimulation and DRGS. Stimwave technology has a wide spectrum of stimulation parameters available for clinical applications which include: Amplitude: 1 - 24 mA, pulse Width: 10 - 1000 microseconds, Frequency: 5 - 20,000 Hz.

The Apparatus

Patients are implanted with one or more stimulation systems containing 4-8 contacts which are 3 mm in diameter kept at a distance of 4 mm from one another (Figures 1,2). The stimulator has an implantable electrode array, a microprocessor and a receiver for antenna, powered by an external power generator (EPG, Figure 3). The only component that gets implanted is the miniature electrode which is passive and wirelessly operated by the EPG/transmitter that is worn by the patient over a single layer of cloth. The implanted electrode receives the desired stimulation from the EPG via a Radio Frequency (RF) transmitting antenna through the wireless receiver [49]. This device uses RF energy of 915 MHz to transfer power and selected stimulation parameters as indicated for clinical use by the physician.

DISCUSSION

Clinical experience with SCS has shown that securing analgesia in patients with chronic back pain could be very frustrating [50-53]. Several studies with HF systems have demonstrated the efficacy in providing relief in cases of chronic intractable back pain [3,19,48]. However, the SCS system apparatus itself is still not devoid of the complications related to the implantable power generator and the paraphernalia like the connectors, lead extensions. Kumar et al reported device related complications in 32% of patients [54]. Surgery was performed in 12% cases for hard ware related complications. Senza trial reported that 4% HF10 therapy subjects and 7.2% of conventional SCS subjects had serious adverse events (P = 0.3) and 27.7% and 33% non-serious study related adverse events respectively. Lead migration required surgery in 3% of HF10 and

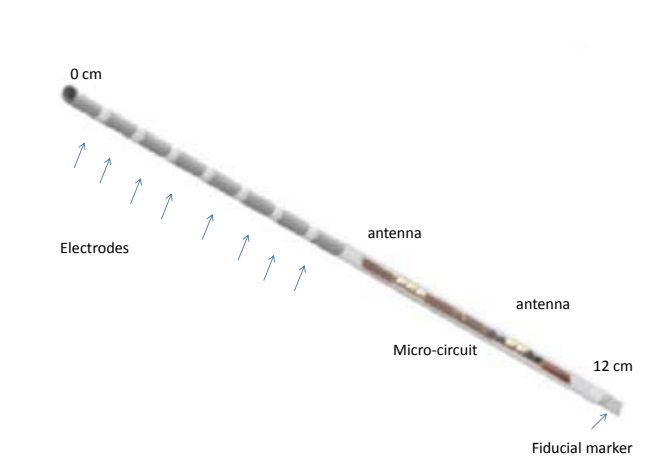

Figure 1: Neuro-stimulator electrode; MRI compatible; for both 1.5 and 3 Tesla.

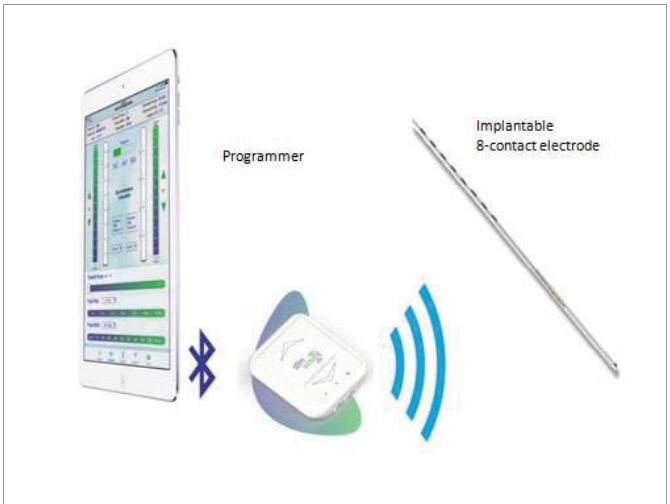

Figure 2: Neurostimulator receiver.

Figure 3: WAA.

5.2% of traditional SCS patients [3]. It is noteworthy that patients in Senza trial and other studies did not experience serious adverse events related to stimulation parameters. HF stimulation per se does not seem to result in any unique complications or side effects related to the frequency [3,19,20]. Additionally, HF stimulation provided paresthesia-free analgesia and appears to be paresthesia independent. There is also possibility that midline positioning of the contacts on the stimulating electrode may not be a significant technical factor in providing pain relief with HF stimulation, as reported recently in a prospective multicenter trial [57]. We accumulated our experience with HF stimulation in 37 (30 for SCS and 7 for DRGS) patients so far and no one had any adverse events related to the implant, which was an electrode only. All of them had sustainable analgesia. The wireless neuromodulation does not employ any implantable power generator or additional wiring/extension cables and thus these patients had no implant-related complications. The implantation procedure requires a small incision only since it is percutaneous and minimally invasive, to place the electrode. No additional implant is needed for therapy and hence provides the comfort as well as cosmetic results apart from lowering the costs of surgery and postoperative pain. The likelihood of adverse events is minimal while patients attain therapeutic goal of analgesia [55,56]. Device malfunction, stimulation failure and lead displacement occurred in few cases requiring revision of the implant. Our outcomes and experience are as good as and often better than wired stimulators unless stimulation moves with migration or the device becomes damaged somehow from too shallow of a placement. The simplicity of the neuromodulation apparatus is very much to the advantage of compromised situations where patients have limited life expectancy or terminal illness, reduced immunity and retroviral infections. Complications with the existing technology have been hampering the progress of neuromodulation and the wireless device describes above, promises to enhance rapid evolution of the therapeutics.

Perspective

Wireless stimulation in our experience has been as good as the wired stimulation or even better unless stimulator placement, due to technical and anatomical differences, was shallow. Frequencies either low or high did not produce serious adverse events as far as the current experience with spinal cord stimulation is concerned. In experimental models, even at the highest intensity and frequency most animals do not exhibit complete reversal of the mechanical hypersensitivity. There are always non-responders to the protocol at all frequencies and intensity of stimulation. A pre-lesion response is not attainable with any combination of stimulation parameters. This is very similar to the clinical scenario where SCS can yield only a partial pain relief that is compatible with comfort and daily activities. Most protocols keep the relief at “above 50% improvement” for significant clinical response. Hence, there is always scope for improvement in the methods and technology we apply to achieve better analgesia with SCS, today. Minimally invasive procedures, wireless stimulation and external power generators are steps to reach this goal. Several studies are at present ongoing and multicenter, randomized controlled trials shall establish the safety and efficacy of this wireless neuromodulation method.

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