



Neuromodulation: Origen, Evolution and Evidence

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Abstract

Since Roman times, humans have been fascinated with the use of electricity. Over centuries, multiple well-known scientists tried to use this physical element to address a number of neurological conditions. However, they did not have a clear understanding of how to use it. In 1965, two brilliant investigators, Patrick Wall and Ronald Melzack, postulated the gate control theory, which gave rise to the field of neuromodulation. Over the years, this field has evolved exponentially, and is now becoming a main tool for interventional pain physicians addressing chronic pain, as well as the current opioid crisis. Despite multiple randomized control trials, the recurrent question of whether there is enough evidence to determine how effective the therapy is still remains. Our article attempts to answer this question while reviewing the progression of the field over the years.

Introduction

For the purpose of this review, we will borrow the definition of neuromodulation from Dr. Philip Gildenberg as “electrical stimulation of the nervous system for the purpose of modulating or modifying a function, such as the perception of pain” [1]. In his article, Dr. Gildenberg dates back the use of electricity to ancient Rome, when Scribonius, in 15 AD, recommended the use of the torpedo fish to treat such malaise as gout arthritic pain. Over the following centuries, other well-known scientists became fascinated with electricity. Such scientists include, Benjamin Franklyn, Galvani, and Mary Shelly, who wrote the famous novel Frankenstein in 1816 inspired by the work of Dr. Erasmus Darwin, Charles’ grandfather [1]. During the late 1800’s, the first commercially available device for the application of electricity came to market. It was called Electro treat, and its use included not only the treatment of pain, but all kinds of maladies [1].

The Science of Neuromodulation

In 1965 two brilliant scientists, Patrick Wall and Ronald Melzack wrote a paper in the journal Science, in which they tried to explain the transmission of pain, as well as how it is modulated by activation of large fibers. It was called the gate control theory, and it opened up the doors for the emerging field of neuromodulation as treatment of pain [2].

Dr. Wall put his own theory to the test with the help of Dr. William Sweet. After stimulating their own infraorbital nerves with a percutaneous electrode, they recruited 8 patients with intractable pain secondary to peripheral nerve injuries and found that most of them experience temporary relief of symptoms [3]. This report is considered the birth of the field of neuromodulation.

While Sweet and Wall worked on the peripheral nerve stimulation, another neurosurgeon, Dr. Norman Shealy, decided to apply the gate control theory by stimulating the dorsal column, “where the large nerve fibers are uniquely gathered” [1]. Shealy implanted electrodes in the dorsal column of a patient dying from bronchogenic cancer with possible metastases to the pleura and liver. His report was published in Anesthesia & Analgesia in 1967, and described how this poor patient got a few hours of pain relief at a time with the application of electrical current to the electrodes implanted into his thoracic spine [4]. Subsequently, Dr. Shealy, working with an engineering student from Case Western by the name of Thomas Mortimer, developed a more sophisticated electrode, and with the help of a small company at the time working on developing cardiovascular stimulators, developed the first spinal cord stimulator.

Over the years, spinal cord stimulators became more sophisticated, and eventually percutaneous electrodes became available, opening up the field for non-surgical pain providers.

The Evidence

As the field continued to grow, there was a need for more evidence to confirm the effectiveness of SCS in treating chronic pain. In the 90’s, multiple retrospective studies were published, but it

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was not until the year 2000, when Kemler, et al. [5] published the first randomized control study on the use of Spinal Cord Stimulation (SCS) for the treatment of Complex Reflex Sympathetic Dystrophy [5] that we had stronger evidence of the effectiveness of this therapy. This study, however, became controversial after a meta-analysis performed a few years later by the author showed that patients were losing relief of symptoms after two years [6]. Still, other authors were able to confirm the utility of this device for the treatment of failed back surgery syndrome [7,8], as well as diabetic neuropathy [9-11]. Over the following years a plethora of innovative techniques and waveforms started to emerge [12-14], all related to the fact that up until then, we were only using what we now call tonic stimulation, which consisted of using low frequencies (around 60 Hz), and higher amplitudes causing patients to feel paresthesia's in the target region of their body. This type of stimulation makes it difficult to address one of the major complaints of patients: axial back pain. In order to address axial back pain, electrodes, up until then, had to be implanted at the physiologic midline of the dorsal column, in order to avoid recruitment of dorsal roots, which will cause painful paresthesia either on the chest wall, or the abdomen based on the spinal level where the electrodes were implanted. Additionally, patients with a peripheral injury (i.e. CRPS or diabetic neuropathy), were feeling paresthesia in non-painful areas of the limb that was target, which was also uncomfortable [15-17].

The beauty of the new waveforms was that by using "high frequencies" with lower amplitudes (subthreshold stimulation); patients would not be able to feel paresthesias, hence, improving coverage for back pain, even when the electrodes were not placed exactly at midline. Additionally, the ones with peripheral injuries would not feel paresthesias in non-painful regions of their limbs.

One of the first of these new devices was simply called high frequency stimulation or HF10 [12]. Its popularity grew after the publication of the first randomized control study comparing the new therapy with traditional tonic stimulation [18]. The Senza study was primarily a non-inferiority study and secondarily a superiority study comparing HF10 with traditional tonic stimulation in patients with intractable back and leg pain. A total of 198 patients were randomized in a 1:1 ratio to a treatment group across 10 treatment centers. At 3 months, 84.5% of implanted HF10 therapy subjects were responders for back pain and 83.1% for leg pain, while 43.8% of traditional SCS subjects were responders for back pain and 55.5% for leg pain ($P < 0.001$ for both back and leg pain comparisons). The device not only demonstrated non-inferiority, but also superiority over traditional tonic stimulation.

Not very long after the emergence of HF10, Dr. De Ridder, published his work on a new waveform he called, burst stimulation [13]. This new waveform consisted of short bursts of high frequency stimulation at 500 Hz, delivered at a rate of 40 cycles per second. The advantage of this model is that it consumes less energy than HF10, so that patients do not need to charge their batteries (IPG) as often. This waveform was also tested on a randomized control trial called SUNBURST [19], in which 100 subjects were randomized to receive 12 weeks of traditional tonic stimulation followed by another 12 weeks of burst stimulation. There was no washout period in between the two modalities. It was also a noninferiority study and it again showed burst as not only noninferior to traditional SCS, but actually superior.

Strength of Evidence

Despite the emergence of more randomized control trials, questions still remain pertaining to the effectiveness of this therapy. One of the major criticisms of neuromodulation has always been the lack of sham studies. In the past, the excuse was that it was impossible for patients not to feel paresthesias when the device was on. However now, with the emergence of "subthreshold stimulation" that excuse is no longer valid. To be fair, Dr. De Ridder initial work did include a sham group, but his study only consisted of 15 patients [13]. Another important issue is that all major randomized studies have been industry-sponsored studies, which as we know, have the tendency of being favorable to their products.

Additionally, up until now, we do not have a clear understanding as to how these therapies work, or what are the indications to use one or the other.

Again, Dr. De Ridder did propose that burst stimulation works on the medial pain pathways suggesting that it modulates the affective component of pain; however, his work, had not been reproduced by anyone, and no studies assessing the effectiveness of burst in patients with emotional pain has ever been done.

There is hope, however. Independent investigators are starting to question the results of these large studies and are performing their own [20-23], which have found controversial results.

Perruchoud et al. [20] and De Andres et al. [21] both compare high frequency stimulation with tonic stimulation in double blind studies. In both cases, they were unable to find any difference in outcome between the two modalities. In the case of Dr. Perruchoud study, he used patients that had been previously implanted with traditional tonic stimulation and having a good response to the therapy. He then, randomized them to receive either sham stimulation or high frequency stimulation. The patients receiving high frequency stimulation did not separate from the ones using sham. The study was criticized because patients were already used to tonic stimulation, and had good results, so that there was no incentive for them to switch therapies. In addition, the frequency used was only 5000 Hz and not 10,000, as the commercially available high frequency system uses. Finally, the leads were implanted following traditional paresthesia mapping, and not necessarily at the T9/T10 level as the HF10 requires.

Dr. De Andres study [21], enrolled patients that were having back and leg pain after diagnosis of Failed Back Surgery Syndrome (FBSS), and randomly assigned them to have either tonic stimulation or high frequency stimulation. The implanter was unaware as to the group each patient belongs to up until the time of the procedure. In addition, the person collecting the data was also blinded to the subject's group. Patients were told that they may feel stimulation or not, but in any case, both systems were equally effective. The results of the study once again showed no separation between tonic and high frequency stimulation patients.

Also, Drs. Thomson and Al-Kaisy performed studies looking at the rate of stimulation [22,23]. The so call PROCO study was a randomized controlled trial in which Dr. Thomson et al. [22] look at different frequencies (1, 4, 7 and 10 KHz), assuming that they will all work the same, and found no difference among them [22]. A major drawback of the study was that there was no control group, so that we are unable to tell if any of these frequencies will separate from sham stimulation. On the other hand, Dr. Al-Kaisy's study did include a

sham group. He enrolled patients with diagnosis of FBSS who have failed conservative management. They all received a traditional stimulator for the trial, and those who got 50% or more relief were implanted. After implantation, there was a 4-week washout period and then, they were randomized to receive sham stimulation, 1200 Hz, 3030 Hz or 5882 Hz for three weeks each [23]. The results were surprising: none of the frequencies used separated from sham except the 5882 Hz. Sham itself caused a drop in the baseline VAS of 3 points. The difference between the higher frequency and sham was only of 1.6 points, causing the authors of the study to question the clinical significance of this difference.

Conclusion

In summary, as the field of neuromodulation continues to mature, and new technologies become available, investigators will need to seek alternative sources of funding, in order to perform more independent studies that will provide better quality data and would allow us to determine the true effectiveness of these procedures.

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