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Multi-target neurostimulation for adequate long-term relief of neuropathic and nociceptive chronic pain components

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Abstract

Successful treatment of chronic pain for patients with failed back surgery syndrome can be extremely complicated. These patients require careful and individualized clinical assessment, as they often present with mixed pain syndromes that involve both neuropathic and nociceptive components. The distinct types of pain involved in such cases may require combined treatments from individual interventions that are analgesically independent and specific for each type of pain involved. Neuromodulation by electric stimulation at appropriately chosen targets and combinations may be an important option to consider for such patients. We present a case of combined debilitating axial nociceptive spinal pain and bilateral neuropathic leg pain in a patient after 14 failed back operations. A combination of spinal cord stimulation (SCS) and deep brain stimulation in the periventricular gray (PVG) have successfully provided the patient with complete relief of both components of his chronic pain condition, after all other pain management options had been exhausted. By alternating activation of each implanted stimulator separately and in conjunction, we were able to demonstrate a clinically independent analgesic character for each stimulation system, each specific to a particular type of pain. The SCS provided complete relief of the neuropathic pain component, without affecting the nociceptive component at all. The PVG stimulation provided complete relief of the nociceptive component, without affecting the neuropathic component at all. In combination, there was complete relief of the total chronic pain condition. There appeared to be no overlapping or synergistic effect between the two neuromodulation systems in the patient. The patient has had prolonged complete relief from his chronic pain condition with the combined neuromodulation intervention over 22 years of follow-up.

Key Words: Chronic pain, deep brain stimulation, failed back surgery syndrome, periventricular gray, spinal cord stimulation

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INTRODUCTION

Pain is usually categorized as either somatogenic or psychogenic. Somatogenic pain, or organic pain, arises from somatogenic lesions resulting from trauma, infection, or other external factors.[2] Somatogenic pain is divided into two main categories: nociceptive and neurophatic pain. Nociceptive pain refers to pain

originating via stimulation of peripheral nociceptors, or pain receptors. Nociceptive stimulation then transmits signals to the central nervous system through integral somatosensory pain pathways, causing a person to experience pain.[12] Neuropathic pain, or deafferentation pain, refers to pain following direct damage to the nervous system. Neuropathic pain can be classified as either peripheral (i.e., dysesthesia dolorosa, phantom-limb pain, diabetic neuropathy) or central (i.e., spinal cord injury, poststroke pain, postherpetic neuralgia).[24]

In the treatment of pain using deep brain stimulation (DBS), target selection is guided by the specific type of pain being treated. DBS treatment for pain of nociceptive origin predominately entails stimulation of the central gray matter, either the periaqueductal gray (PAG) matter or the periventricular gray (PVG) matter.[32] The sensory thalamus has been the principal target region for DBS treatment of neuropathic pain,[4] specifically the ventral posterolateral (VPL) nucleus or the ventral posteromedial (VPM) nucleus.

The mechanism by which DBS treats pain symptoms is not fully understood. The original studies of Reynolds in rats showed that stimulation of the lateral margin of the PAG matter inhibited nociceptive responses.[34] Further research indicated that this effect was reversible with administration of opioids antagonist.[16] Two studies showed that endogenous opioid levels were elevated in the third ventricle following electric stimulation of the PAG/PVG.[1,18] Other studies reported reverses in pain relief after administration of naloxone.[17,36] Regarding PAG stimulation, there is an additional mechanism involving spinal cord stimulation (SCS). Following stimulation via PAG matter neurons, the medullary nucleus raphe magnus (NRM) projects to the dorsal horn of the spinal cord. Considering that the PAG matter, NRM and dorsal horn of the spinal cord all contain high levels of opiates, analgesic effects via stimulation are likely to be mediated by these structures.[12] Stimulation of PVG matter leads to increased level of endogenous opiates and may alter a patient's psychogenic response to pain.[2] Despite evidence of efficacy, DBS remains off-label for chronic pain management in the US.

SCS is the caudal analogue of VPL stimulation for the treatment of bodily neuropathic pain. Failed back surgery syndrome (FBSS) is the most common indication for SCS in the US. Its mechanism of action is also based on Melzack and Wall's gate control theory of pain.[26] SCS might relieve pain by blocking the conduction of primary afferents at the branch points of dorsal column fibers and their collaterals.[6] Dorsal column activation is more successful than ventral stimulation, which is close to the spinothalamic tracts.[22] Mechanical or nociceptive axial low back pain does not respond as well to SCS, in contrast to neuropathic pain.[23,27] SCS is a valid alternative to reoperation in FBSS patients.[29] SCS is also less expensive than conventional medical pain therapy for FBSS.[3,19]

The term "FBSS" is sometimes confusing. FBSS is in fact not specific to a particular pain diagnosis, but is merely a general term that refers to situations of persistent chronic pain following spinal surgery. In reality, FBSS in patients is commonly found to be a mixed pain syndrome consisting of both neuropathic and nociceptive components. The potential importance of multi-target implantation for patients with mixed nociceptive/neuropathic pain syndromes is known, and it has been reported that these patients may be best treated with combined implantations of the PVG/PAG and VPL/VPM targets.[42] However, to our knowledge, the potential benefit of a combination of SCS plus DBS of the PVG in the treatment of FBSS has not been reported. Below, we report such a case, where over 20 years of complete pain relief has been achieved with dual SCS and PVG stimulation in a patient who presented with debilitating neuropathic bilateral radicular leg pain and nociceptive axial lower back pain after 14 prior failed back operations.

CASE REPORT

A 46-year-old male patient (MP) presented to our neurosurgical pain clinic in 1989, with complaints of extreme intractable chronic pain of the lower back and in both legs. MP's prior surgical history included 14 spinal surgical procedures, including decompressive procedures, fusions, scar tissue removal for postsurgical epidural fibrosis, facetectomies, and laminectomies at multiple levels. Prior to coming to our clinic, in an attempt to manage his chronic pain condition, MP had been tried on multiple block injections, transcutaneous electrical nerve stimulation (TENS), narcotics, antidepressant, antianxiety, and sedation medications, in addition to physical therapy and rehabilitation programs. Intradural morphine was trialed, but had to be discontinued because it failed to produce meaningful analgesia and furthermore MP developed urinary retention and pruritus with this intervention. Eventually, MP was placed in hospice care under heavy sedation by pain management physicians for an apparently hopeless intractable pain situation.

On examination, MP was found to be arreflexic with dermatomal hypoesthesia in legs and arms. Straight leg raise test was positive at 30°, bilaterally. There was mild weakness in dorsiflexion of both feet, and generalized mild weakness of both legs. However, the motor examination was limited due to suboptimal cooperation by the patient, secondary to severe pain. MP's worst complaints were of intractable lumbar and bilateral leg pain.

The lumbar pain in general was continuously relentless, and excruciating, and was further exacerbated by any activity, including sitting, standing, walking, and valsalva maneuver. The leg pain worsened with standing,

walking, and showed claudication. Besides exhibiting dermatomal hypoesthsia, sensation in either leg showed areas of allodynia and hyperpathia. However, there was no evidence of sympathetically mediated pain, or of any trophic changes. Anal sphincter tone was good and there was no incontinence, although there was a history of urinary dribbling and a subjective sensation reported of incomplete bladder emptying after urinating.

MP was diagnosed as having a mixed pain syndrome, composed of a neuropathic radicular component in both legs plus a nociceptive component in the lower back, secondary to FBSS.

Under our care, MP first underwent SCS, using a single Medtronic paddle "Resume" (Minneapolis, MN) stimulator placed epidurally at the midline at T10, T11, and T12 through laminectomies [Figure 1]. Excellent bilateral pain relief was achieved, however, axial lower back pain remained. Since the SCS provided no benefit for the back pain, a decision was subsequently made to implant a DBS of the PVG on the nondominant sphere. For the DBS, a single medtronic brain electrode(s) was stereotactically implanted in the PVG, utilizing a Leksell (Atlanta, GA) stereotactic frame with CT guidance [Figures 2 and 3]. The DBS procedure achieved excellent axial spinal pain relief. The current stimulation parameters are as shown in Table 1.

Over these past 22 years, MP has been closely followed. Whenever both SCS and DBS neuromodulation systems were operating and utilized simultaneously, complete relief of back and leg pain has been maintained. However, electrode programming adjustments have been carried out as necessary, such as after accidental exposure to magnetic fields or after generator battery depletion. In addition, wire-connector revisions were twice required after motor vehicle accidents.

During each reprogramming visit, the generators for each of the SCS and DBS were turned on or off separately and in combination. An independent programming technician would operate this alternating activation, while the patient and physician remained uninformed as to which system was on or off at the time. The testing was carried out in this fashion to protect against a possible placebo effect or other external factor that could bias observed analgesic effects. Additionally, at least twice a year, subthreshold stimulations were carried out by other physicians who were blinded to the optimal programming of the systems; independently and consistently, there was complete correlation among the various physicians, patient response, and visual analog pain scaling with each programming variation.

These tests showed specific and independent analgesic effects of the two implanted neuromodulation systems. The SCS induced analgesia specifically for the neuropathic bilateral leg pain, and produced no benefit on its own for the nociceptive axial spinal pain. Conversely, the PVG DBS stimulation was specific for the nociceptive lumbar pain and, on its own, had no effect at

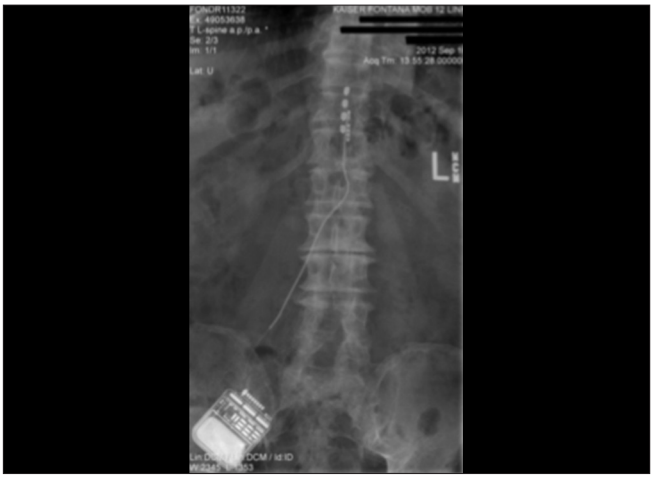

Figure 1: X-ray showing spinal cord stimulator system implanted trough thoracic laminectomy

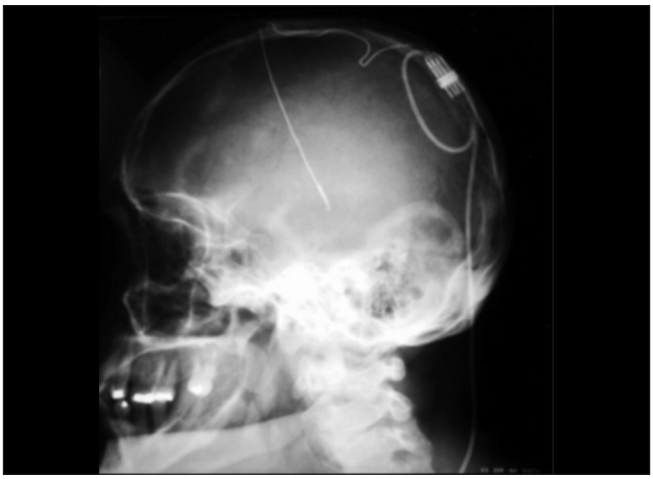

Figure 2: Brain electrode and connecting wires (circa 1980's system) at PVG target, lateral view on plain film X-ray

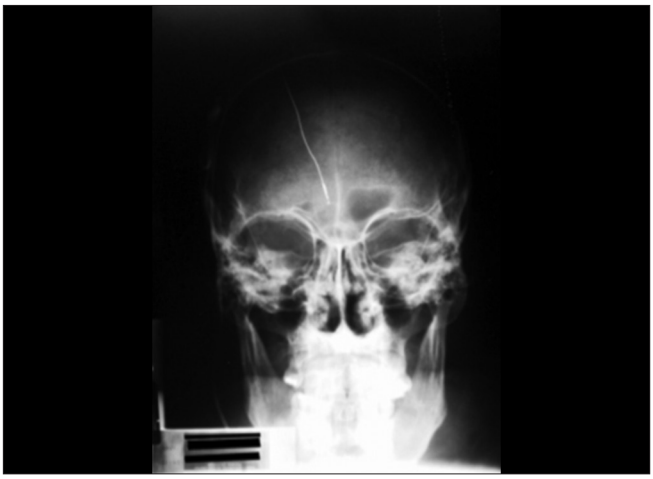

Figure 3: A.P. view of dbs implant at pvg shown by plain film X-ray

Table 1: Current stimulation parameters of combined DBS and SCS achieving pain relief in patient MP

DBS parameters	SCS parameters
0-negative (most distal electrode contact) to case	0–, 1–, 2+, 3–
Volt: 0.3	Volt: 1.2
Pulse width: 60	Pulse width: 270
Rate: 185	Rate: 125

DBS: Deep brain stimulation, SCS: Spinal cord stimulation, MP: Male patient

all on the leg pain. Whenever both systems were off, both nociceptive and neuropathic pains were excruciating, rated as 10/10 by the patient. Whenever both systems were on with optimized stimulation programming, the patient consistently reported pain as 0/10.

Aside from the intermittent stimulator adjustments that were required over the years, MP's chronic pain condition has been completely controlled with the neuromodulation intervention for the past 22 years. He has been able to return to living a normal life without interference by chronic pain in his activities. He no longer goes to physical therapy/rehabilitation, no longer takes any medication for chronic pain, and is no longer followed psychiatrically. MP's pain is currently controlled only with combined SCS/PVG-stimulation.

DISCUSSION

The concept of using targeted electrostimulation of the nervous system to treat pain conditions originated in the 1950s in the works by Heath and Pool.[15,31] In the current era, it has been observed that electric stimulation in various anatomical zones of the nervous system, including deep brain structures, motor cortex, spinal cord, and peripheral nerves, offer the possibility of analgesia for certain pain patients.[37]

Despite an over 50 year history of use and development as a modality for pain treatment, definitive efficacy, clear clinical standards, and guidelines for electric neuromodulation practice have not yet been unequivocally demonstrated in the literature.[8,21,33] The published evidence supporting use of one technique over another, such as DBS versus MCS versus SCS, or one target over another, such as PVG versus thalamus in DBS, remains relatively scant and may thus be controversial in given cases. It is most likely the case that each stimulation option, or combination of several options, has its place as the most appropriate in different situations. In DBS, for instance, PVG/PAG has arisen as a preferred target over the VPL/VPM nuclei for treating nociceptive pain states. However, in cases of neuropathic pain, the thalamic nuclei are preferred over the PVG/PAG.[42]

Of course, in addition to pure analgesic efficacy, the particular surgical invasiveness and risks of technique and target must be a factor in choosing the most appropriate neurostimulation intervention in a given case. For instance, SCS and VPL stimulation may have overlapping mechanisms and therefore either might be indicated for neuropathic pain.[13,14,37] Nevertheless, it should be kept in mind that SCS can be trialed using minimally invasive percutaneous techniques, while trialing DBS requires that a full intracranial stereotactic procedure be carried out from the start. DBS therefore also always runs the risk of intracranial bleed (1-5%).[35] From an additional perspective, consider also a situation of bilateral neuropathic radicular pain, as was the case of the patient MP. In such a case, bilateral thalamic stimulators would need to be implanted for DBS to succeed, as opposed to the reasonable likelihood that a single midline SCS could provide neuropathic analgesia to both legs, as occurred with MP.

Therefore, SCS involves a simpler and less risky operation than DBS. For that reason, in patients with a radicular neuropathic component to their pain that theoretically could benefit from either SCS or DBS, SCS should be trialed before opting for thalamic DBS. Nevertheless, a specific indication for thalamic stimulation might otherwise occur after failure of an SCS trial or implant. In such cases, bilateral thalamic stimulators would be needed to control bilateral neuropathic leg pain. In contrast to DBS for neuropathic pain, when treating nociceptive pain with DBS, using just a single stimulator in the PVG has been sufficient in our experience.

Successful neurostimulation outcomes fundamentally depend on strict patient selection with correct choice of stimulation target. Careful clinical classification of the patient's pain syndrome (i.e., nociceptive or neuropathic) could be the determining factor toward success of neurostimulation, since subtle diagnostic distinctions could imply optimal target choice. However, largely due to the scarcity of objective signs and the general subjective nature of the patient's complaints, the appropriate assessment, diagnosis, and intervention for intractable pain disorders can be extremely complex.

The location, type, intensity, and analgesic response to other pain control modalities are solely sensed by the patient. The thorough clinical assessment of pain is highly contingent on the patient's subjective descriptions of these aspects, which in turn can be variably influenced by many difficult to control factors. As Coffey and Lozano have said, "the paradox of pain – its simultaneous reality and subjectivity – makes the assessment of pain relief therapies susceptible to observer- or patient-related influences."[8] Thus, diagnosis of specific pain syndromes and pain types is difficult, and always relies on good clinical judgment.

A commonly used tool to quantify pain states before and after therapy is the visual-analog pain scale (VAPS). It

is considered a reliable marker of a particular patient's pain state, and is commonly used to assess analgesic response to treatment or a possible placebo effect. However, because of the inherent subjectivity of pain, we remain limited in our ability to depend on VAPS for precisely assessing pain states, as it is a unidimensional pain scale.[44] VAPS still depends on subjective patient reporting and, furthermore, VAPS cannot automatically distinguish among the different possible components/types of pain. VAPS is thus still a far from perfect tool. Interpretation of the clinical meaningfulness of VAPS scoring remains necessary.

Probably because of the inherent complexity involved in the clinical assessment of medically intractable pain and how clinical consideration of these patients must be carefully individualized, it is of no surprise that, as Wallace and Levy point out in their respective reviews of the literature on DBS for pain, there is a significant lack of standardization regarding definitions of successful outcomes and the tools used to assess the outcome measures.[21,42] Thus, it has been difficult to compare methods and outcomes across studies. Drawing general conclusions regarding the most appropriate neurostimulation modality, target, and/or combination for particular cases are still difficult to do based on the literature at this time. Fortunately, the shortcomings of the literature to date have already been pointed out by other authors, and the goal to conduct better standardized, controlled, and comparable trials has been set.[8,21,42]

Additionally, the prevalence of possible mixed nociceptive and neuropathic syndromes in patients is another reason to carefully individualize management of pain patients, both out of concern for individual patients, as well as from a public health perspective. FBSS is a relatively common presentation of a mixed pain condition. The epidemiology and demographics of FBSS, and back pain in general, highlights the importance of carefully assessing these mixed pain conditions for choosing the most appropriate interventions.

It has been reported that low back pain in general has a point prevalence of 37%[38] and a lifetime prevalence between 65% and 85%[30,38] among adults. It is estimated that the direct healthcare costs of low back pain are between 12.2 and 90.6 billion dollars per year in the US.[9] The indirect costs of back pain, in terms of lost productivity in the US workforce, have been estimated to be 19.8 billion dollars per year.[39] The use of various types of spine surgery for low back pain, particularly lumbar spinal fusion, has been on the rise for several decades, however, often without clear indication.[11] Chan and Peng argue that rates of spine surgery may be particularly excessive in the US.[7] Between 10% and 40% of patients will develop FBSS following lumbar spinal surgery.[20,28,43] Together with the aforementioned rise in number of spine surgeries in recent years, not surprisingly an increase in number of patients with FBSS has also been observed.[5,7,25,40] Without including further surgery or implantation of neurostimulators or intrathecal pumps, the direct costs of medical therapy for FBSS is estimated at over $18,000 per patient per year in the US.[10]

Individual patients with FBSS may suffer with very significant overall morbidity. It has been reported that patients with severe FBSS experience greater levels of pain, lower quality of life, greater disability, a higher rate of unemployment (78%), and a higher rate of anxiety/depression, as compared with other chronic pain conditions such as osteoarthritis, rheumatoid arthritis, complex regional pain syndrome, and fibromyalgia.[7,41]

It is clear that careful and appropriate management of FBSS patients is a significant concern. It is important to remember that FBSS is not a specific diagnosis. Failed backs are not all the same and, in fact, FBSS patients often have such mixed pain conditions. Available treatment modalities may be specific for particular types of pain. The demonstrated independent analgesic effect of SCS for the neuropathic component, and PVG DBS for the nociceptive component is illustrated in patient MP's particular case of FBSS. As it was in the case of MP, combined multi-modal (i.e., both SCS and DBS) or multi-target (i.e., PVG/PAG and VPL/VPM) neuromodulation may be necessary for some patients with mixed chronic pain conditions. The use of just one target may be inappropriate or inadequate, and thus the patient may continue to report extreme and debilitating pain.

In summary, when noninvasive treatments for FBSS patients have proven inadequate, consideration should be given to specific neuromodulation alternatives. However, it should be kept in mind that not all failed backs are the same, and that one or another neuromodulation modality on its own may fail. However, combing them may rescue some carefully selected patients.

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