Curr Pain Headache Rep
DOI 10.1007/s11916-012-0276-9

CANCER PAIN (DA MARCUS, SECTION EDITOR)

Spinal Cord Stimulation in the Treatment of Cancer-Related Pain: "Back to the Origins"

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Abstract Spinal cord stimulation (SCS) has been used in the treatment of chronic pain for more than 40 years. The most common indication for SCS in the USA is failed back surgery syndrome (FBSS). Interestingly, the first two spinal cord stimulators ever implanted were in patients suffering from bronchogenic carcinoma and pelvic cancer, respectively. While cancer accounts for millions of deaths each year in the USA, pain is often the first sign of malignancy. An increasing number of people suffer from cancer-related pain each year and many receive suboptimal relief. Given the demonstrated value of spinal cord stimulation in the treatment of neuropathic pain, spinal cord stimulation should be considered "earlier" as an adjunct to the treatment of cancer-related pain. In addition, with the improving survival rates associated with advances in cancer treatment, spinal cord stimulation may help reduce the risk of development of chronic neuropathic pain in survivors.

Keywords Spinal cord stimulation · Cancer pain · Neuropathic pain · Implantable technologies

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Published online: 19 May 2012

Introduction

Cancer accounts for approximately 6.6 million deaths each year. Pain is often the first sign of malignancy, and its prevalence at diagnosis has approached 50 %. Approximately 9 million people suffer from cancer-related pain each year [1]. Three of every four patients experience moderate to severe pain in the advanced stages of their disease [2]. Approximately 10–15 % of patients with cancer-related pain achieve suboptimal pain relief with opioids alone or in combination with conventional adjuvant analgesics [3].

Neuropathic pain (NP) is a complex process involving maladaptive mechanisms and neuroplastic changes in response to nervous system injury resulting in chronic pain. Neuropathic cancer pain (NCP) is a similar process that affects patients with malignancy. NCP afflicts approximately 15–40 % of patients with malignancy [4]. Various pathophysiological mechanisms and treatment options have been described, and are discussed in detail later.

World Health Organization (WHO) guidelines for the treatment of cancer pain have been established as a three-step ladder of treatments as follows: Step 1: nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and acetaminophen for mild to moderate levels of cancer pain; Step 2: weak opioids for mild to moderate pain that does not respond to NSAIDs alone; and Step 3: strong opioids for moderate to severe cancer pain [5]. Adjuvant medications, such as antiepileptics and tricyclic antidepressants, can also be added at any step of the ladder for optimal pain relief. While such guidelines are well intentioned, patients suffering from cancer pain are often failed by such treatments, either due to suboptimal pain relief or intolerable side effects.

Spinal cord stimulation (SCS) is a minimally invasive non-pharmacological approach to neuropathic and nociceptive pain, and has been shown to be an effective analgesic

tool in patients suffering from chronic pain states such as failed back surgical syndrome (FBSS) or complex regional pain syndrome (CRPS). Since its first use for pain control in 1967 by Norman Shealy, multiple studies have demonstrated its efficacy in the treatment of intractable, chronic pain with a variety of causes [6]. There is a growing body of evidence that supports the pain-alleviating effect of SCS for patients with cancer pain.

Mechanisms of Neuropathic Cancer Pain

The ability to detect noxious stimuli is a protective mechanism of most organisms and is essential for survival. Acute tissue injury that leads to chronic pain is associated with neuroplastic changes in the peripheral and central nervous system in response to the nociceptive input. Such changes lead to nervous system hypersensitivity, which, in turn, promotes guarding of the injured area. Persistence of these changes often leads to debilitating chronic pain. Three intertwined processes may serve as targets for the prevention of chronic pain and include peripheral sensitization, central sensitization, and descending modulation [7].

Neuropathic pain tends to arise later in the disease course, but it is also more persistent once neurogenic inflammation and peripheral and central sensitization ensue. Neuropathic pain tends to be associated with dynamic, sharp stabbing painful sensations, whereas nociceptive pain is often described as constant, dull, achy, and squeezing. Neuropathic pain tends to respond less to opioid analgesics when compared to nociceptive pain.

NCP arises from injury to peripheral or central neurons in a similar manner to pain arising from non-cancer nervous system injury. Studies have revealed that the same neural pathways, ion channels, receptors, and neurotransmitters are altered in both conditions; however, the nature of injury, its timing, and coexistence of non-neuropathic pain states sets the two neuropathic pain syndromes apart [8].

Cancer pain may have one or more etiologies involving nociceptive and/or neuropathic pain mechanisms (see Table 1). For example, visceral pain may arise from direct tumor invasion and distention of surrounding structures. Somatic pain may result from capsular stretching and inflammatory tumor mediators. It has been estimated that 15–40 % of chronic cancer pain is neuropathic in nature. Neuropathic pain arises from compression and invasion of nerve tissue from local tumor invasion, as well as neural seeding as with leptomeningeal carcinomatosis and metastases involving the nervous system. Tumor cells may also accumulate in microvascular beds leading to ischemic nerve injury and resultant neuropathic pain. Metastatic spread of disease to the central nervous system and radiation-induced myelopathy may be a culprit behind central neuropathic pain [9]. Pain or dysesthesia affects approximately 40 % of patients with transverse myelitis and is usually the most debilitating complication [10]. Additionally, paraneoplastic syndromes may be associated with neuropathic pain. Furthermore, iatrogenic causes for neuropathic pain in cancer patients include untoward sequelae from surgical debulking (postsurgical neuropathic pain), radiation treatments (i.e., radiation plexitis, neuritis, etc.), and chemotherapy (i.e., chemotherapy-induced peripheral neuropathy).

Table 1 Etiologies of cancer pain

Neuropathic cancer pain	Nociceptive cancer pain
Direct tumor invasion	Direct tumor invasion
Leptomeningeal carcinomatosis	Distention of capsular tissue
Microvascular neural ischemia	Cancer-associated inflammatory mediators
Nervous system metastases	Vertebral compression fracture
Central pain	
Paraneoplastic	
Mononeuritis multiplex	
Iatrogenic	
Surgical debulking	
Radiation-induced neuritis, plexitis, myelitis	
Chemotherapy-induced peripheral neuropathy	

Postulated Mechanism of Action of SCS in Neuropathic and Nociceptive Pain

There are two major mechanisms through which pain manifests in cancer patients. The pain associated with the "mass effect" cancer involving visceral organs is mediated through both nociceptive and neuropathic mechanisms; metastatic bone pain is mediated predominantly via nociceptive mechanisms, and pain secondary to involvement of the neuraxis or peripheral nervous system is neuropathic in nature.

Norman Shealy implanted the first spinal cord stimulator shortly after the propounding of the "Gate Control Theory of Pain" by Melzack and Wall in 1965. For many years thereafter this theory served as the model to explain the mechanism of action of the spinal cord stimulator. The theory proposed that a "gate" exists in the dorsal horn of the spinal cord that governs the transmission of nociceptive signals from sensory afferents, through the spinothalamic tracts to the higher centers for the perception of pain. The nociceptive afferents Aδ and C fibers form synapses onto the projection neurons of the spinothalamic tracts in the dorsal horn of the spinal cord which transmits painful signals to the higher centers, by "opening the gate" when stimulated. The large myelinated Aβ fibers carrying non-

nociceptive sensory input (joint position sense, vibration sense, and touch, etc.), when stimulated at the same region, result in the "closure" of the gate. However, it has become increasingly clear that the Aβ mediated "closure of the gate" is insufficient to explain the mechanism of action of the spinal cord stimulator. The exact nature of the substrate of the gate is as yet undetermined. The theory does not explain why acute nociceptive pain is not blocked by SCS yet chronic nociceptive pain is attenuated nor is sufficient to explain the effect of SCS on pain of vascular origin [11••]. Though the "Gate Control Theory" is insufficient to provide the entire explanation for the mechanism of action of SCS, it has formed the basis for much theoretical and practical investigation. It makes allowance for the high degree of specialization of receptor fiber units, explains the interaction between the two main afferent fiber systems, and emphasizes the importance of central screening, selection of patterned information, and descending control. The most important limitation of the theory is that it does not provide evidence of patterned feedback in the dorsal horn or the discrepancy between stimulus intensity and duration and the sensation of pain evoked by it.

Since the late 1970s increasing animal and clinical studies have helped piece together the mystery of the mechanism of action of the SCS. From the standpoint of spinal neurochemistry, gamma-aminobutyric acid (GABA) and acetylcholine have been shown to play a role in neuropathic pain. Microdialysis studies in rats have shown that spinal levels of both GABA and acetylcholine increase during SCS [12]. One can postulate that gate closure is facilitated by the activation of inhibitory neurons, which may be GABAergic or cholinergic. Findings by Holsheimer suggest that stimulus pulses from SCS most likely target myelinated nerve fibers in the dorsal columns (DC) and dorsal roots and that activation of just a single Aβ fiber is sufficient to induce paresthesia in a dermatome [13]. Therefore, SCS could activate inhibitory interneurons, via activation of Aβ fibers, in the dorsal horn to release inhibitory neurotransmitters. This process ultimately would reduce the excitability response of projection neurons in the spinothalamic tract to subsequent input from nociceptive Aδ and C fibers [11••].

Hoppenstein demonstrated that the posterolateral stimulation of the spinal cord provided effective contralateral pain relief with substantially less current than posterior stimulation [14]. This theory supports the belief that SCS results from direct inhibition of pain pathways in the spinothalamic and not secondary to selective large fiber stimulation [15].

There is growing evidence that SCS provides analgesia in neuropathic pain via antidromic stimulation of sensory fibers to release vasoactive substance and via actions on the sympathetic nervous system [11••, 16]. Studies in anesthetized rats have demonstrated that SCS-induced vasodilation involves the release of calcitonin gene-related peptide (CGRP) from primary afferents, and to be possibly blocked by CGRP antagonists [17]. CGRP release may produce vasodilation by binding to its receptors on vascular endothelial cells, thus inducing nitric oxide release [18].

SCS may also influence vasodilation via actions on the sympathetic nervous system. Wu et al. demonstrated that vasodilation induced by SCS relied on both antidromic activation of sensory afferent fibers and inhibition of sympathetic efferent fibers when the hindpaws of animal models were cooled [19]. A recent comprehensive review by Guan summarizes current understanding of neurophysiology and neurochemical mechanisms by which SCS produces analgesic effects based on recent animal models. Guan concludes that though animal studies thus far have helped to assemble a coherent picture of behavioral, cellular, and molecular processes that allow SCS to moderate neuropathic pain future mechanistic work will help broaden the use of SCS treatment for many patients with pain [20••].

Although SCS is traditionally used for neuropathic and ischemic conditions, a growing number of reports describe its efficacy in visceral disease [21]. Recent literature has demonstrated significant involvement of DC pathways in the transmission of visceral pain syndromes [22]. Several clinical studies have demonstrated that a small lesion that interrupts fibers of the DC that ascend close to the midline of the spinal cord significantly relieves pain and decreases analgesic requirements in patients suffering from cancer originating in visceral organs [23]. Behavioral, electrophysiological, and immunohistochemical methods used under experimental situations in animals demonstrated that DC lesion led to decreased activation of thalamic and gracile neurons by visceral stimuli, suppressed inhibition of exploratory activity induced by visceral noxious stimulation, and prevented potentiation of visceromotor reflex (VMR) evoked by colorectal distention under inflammatory conditions [23].

Thus evidence accumulating from animal and clinical studies support a suggested mechanism for SCS neuropathic pain control through its effects on neurophysiology. This includes the activation of Aβ fibers, which are thought to activate GABAergic and cholinergic inhibitory interneurons which suppress projection via the spinothalamic tracts. Given that visceral pain is also partly mediated via the sympathetic nervous system, modulation of visceral pain may in part be due to the effect of SCS on the sympathetic nervous system via inhibitory interneurons.

Advantages/Limitations

There are several advantages and disadvantages with SCS with regards to the utility of this treatment modality for chronic pain in general and for cancer-related pain specifically.

It is a relatively easy to perform, effective, and safe procedure and is readily reversible in the event the patient loses its pain-alleviating effects. Moreover, if SCS fails to provide the expected level of pain relief, patients are not required to undergo the cumbersome weaning process associated with oral, intrathecal, or epidural pain medications [24].

The advantages to SCS for the treatment of intractable cancer pain include: a trial can test patient response before the patient commits to a permanent implant, implantation of the system is minimally invasive, requiring a relatively minor surgical procedure performed on an outpatient basis, has few side effects, and is readily reversible by explantation, if it loses efficacy or is no longer required.

Following the implantation of the permanent spinal cord stimulator device, patients can travel anywhere and participate in any recreational activities, including swimming. Achieving pain relief with SCS can allow patients to reduce or eliminate their use of narcotic drugs, thus minimizing the untoward side effects most unpleasant to cancer patients being the associated constipation and drowsiness. Ongoing advances in neurostimulator technology give patients more control to adjust the stimulation if their pain changes in location or severity. Advancements in the design of electrodes have facilitated more discreet DC mapping in pain, ultimately resulting in enhanced efficacy. Improvements in rechargeable battery technology ensure a prolonged interval between battery replacements.

In general, the main limitation of this treatment modality is that it is not effective in all patients. Most studies show that about 50–60 % of patients who undergo a trial of SCS experience meaningful pain relief, which is defined as a reduction of pain of at least 50 %, by convention. However, SCS has been used with increased frequency for successful treatment of intractable cancer pain.

As with any chronic pain treatment, there are also a number of potential disadvantages and limitations with SCS in the treatment of cancer pain. SCS does not address the source of the pain. The system is designed to modulate pain signal transmission to the brain, but it does not correct any underlying anatomical problem. A retrospective review of 707 cases found that hardware-related complications were common (38 %) and included lead migration (22.6 %), lead connection failure (9.5 %), and lead breakage (6 %), which necessitated a revision or replacement in these cases. Biologically related complications included pain at the generator site (12 %) and clinical infection (2.5 %) [25•].

The treatment of cancer pain with SCS involves an implant and surgery. As with any surgical procedure and implant, there are certain risks and potential complications. Although most are relatively minor, these risks include allergic reaction to the implanted material, bleeding, infection, pain at the incision site, possible dural puncture with or without a resulting post-dural puncture headache, undesirable

Table 2 Summary of available literature on SCS for cancer pain[a]

Study	Study design	Cases	Diagnosis	SCS outcome: pain reduction	SCS outcome: medication reduction	SCS outcome: complications
Yakovlev and Resch [26]	CS	15	Malignant low back pain; colon CA; anal CA; sacral angiosarcoma	All patients had VAS reduction ≥50 % at 12 months	86 % had reduction	None
Yakovlev et al. [28]	CS	14	Intractable chronic chest pain	All patients had VAS reduction ≥50 % at 12 months	All had reduction	None
Yakovlev and Resch [29]	CR	1	Intractable abdominal pain; Bannayan-Riley-Ruvalcaba syndrome	100 % reduction at 6 months	All had reduction	None
Yakovlev and Ellias [24]	CR	2	Case 1: SCC anus with inguinal mets; case 2: epidural metastatic spread of colon CA (radiation-induced neuropathic pain)	90–100 % reduction at 12 months	All had reduction	None
Cata et al. [30]	CR	2	Radiation-induced painful neuropathy; melanoma; Ewing's sarcoma	All patients had VAS reduction ≥50 % at 4 months	All had reduction	None
Lee et al. [31]	CR	1	Spinal meningioma removal; central neuropathic pain	Patient had VAS reduction ≥50 % at 8 months	Reduction	None
Hamid and Haider [9]	CR	1	NSCCL; radiation-induced myelitis; central neuropathic pain	Patient had VAS reduction ≥80 % at 18 months	Near complete reduction	None
Nouri and Brish [32]	CR	1	Prostate CA; postsurgical neuropathic testicular pain	Patient had VAS reduction ≥80 % at 6 weeks	Complete reduction	None

SCS spinal cord stimulation, *CS* case series, *CA* cancer, *VAS* visual analogue scale, *CR* case report, *SCC* squamous cell carcinoma, *mets* metastasis, *NSCCL* non-small cell carcinoma of the lung

[a] Note the paucity of prospective data evaluating the value of SCS on cancer pain

changes in stimulation may occur over time due to scar tissue formation around the leads, skin breakdown, or loss of stimulation effectiveness. Lastly the current devices are not magnetic resonance imaging (MRI) compatible; therefore, this may preclude patients who require surveillance imaging as a key component of ongoing treatment. A mitigating strategy would be to consider where possible computed tomographic scanning imaging (CT scanning) as an alternative as appropriate.

Literature Review

Overall, prospective literature on SCS for cancer pain is scant when compared to other indications for SCS such as FBSS and CRPS. There are no randomized, controlled trials addressing the efficacy and safety of SCS for cancer pain. However, the available literature on the topic, consisting of case series and case reports, is encouraging. Most recently, Yakovlev and Resch reviewed 15 cancer pain patients who underwent successful SCS implantation for malignant chronic low back pain associated with cancer. Similar results were identified in another review of 14 cancer pain patients who experienced significant pain and medication reduction at 12 months [26]. Several case reports followed suit, with no reported complications (see Table 2).

Conclusions

The use of SCS in the treatment of cancer-related pain represents "A Return to the Origins"; this is an interesting observation as the first two reported spinal cord stimulators implanted by Norman Shealy in March and October of 1967 were in a patient with bronchogenic carcinoma and pelvic cancer, respectively. Both patients experienced significant reduction in pain till end of life. Following the initial interest in the use of SCS as a treatment modality, the device fell into disrepute due to inexperience with patient selection, implantation technique, and evolving device design. However, with the resurgence of interest in the use of the device seen in the late 1980s, cancer patients were no longer considered as a patient population for which the device would find utility in spite of Shealy's early observation. The reason for this is unclear; however, possible reasons could include the fact that there was a growing body of research into the neurobiology of pain, and an increasing understanding of the possible mechanisms of action of SCS may have led to the focus on neuropathic pain conditions. Given the prevalence of neuropathic pain as a component of cancer-related pain, SCS may provide an important tool in the armamentarium of practitioners who treat cancer-related pain. Increasing evidence suggests that the earlier introduction of SCS for the treatment of neuropathic pain may be of benefit [27•]. The current WHO ladder for treatment of cancer pain is an invaluable tool. As a result of the demonstrated value of SCS in the treatment of neuropathic pain, SCS should be considered "earlier" to increase the likelihood of preventing the chronicity of neuropathic pain that is inevitably associated with cancer and to reduce the need for medications that may be associated with untoward side effects (see Table 3).

One of the current important limitations to the use of SCS in cancer-related pain is the fact that once a permanent device has been implanted surveillance MRI are no longer possible; this may limit the number of patients who may qualify for the device. Ongoing advances in the SCS technology may result in MR compatible SCS devices becoming readily available, particularly if the awareness that this patient population can benefit from this treatment modality is heightened, both amongst practitioners and device manufacturers.

There may be a place in the future for drug-eluting devices, including spinal cord stimulators that also have the capacity to deliver analgesics or cancer-related drugs into the epidural space for onward transmission through diffusion to the subarachnoid space and spinal cord. The technology already exists with endovascular stents; thus the

Table 3 Suggested clinical indications and timing of use for SCS treatment in cancer-related pain

Clinical indications	Timing for SCS treatment
Bronchogenic carcinoma	With failure of the Step 2 WHO guidelines
Breast cancer (chest wall pain) with/without brachial plexus invasion	Early in Step 3 of the WHO guidelines—if opioids provide suboptimal pain control
Intra-abdominal cancer	With the onset of opioid-induced side effects from Step 3 (WHO)—if opioids initially provided optimal pain control
Pelvic cancer with invasion of the lumbosacral plexus (i.e., involving lower gastrointestinal or urogenital systems)	
Iatrogenic (i.e., chemotherapy or radiation-induced peripheral neuropathy, nerve injury secondary to debulking procedures)	

SCS spinal cord stimulation

extension to neuromodulation devices should require relatively modest investment in research and development to determine which agents, safety and efficacy, and appropriate patient selection.

Ultimately in the future, the development of non-implanted neuromodulation devices, including spinal cord stimulators, will be the key step in making this valuable treatment modality more widely available to patients worldwide, as the current barrier to the use is the fact that specific training is required for the trial and permanent implantation process. This development will result from growing research into forms of modulation of the nervous system other than electrical and from an increasing understanding as to how electrical activity/energy can be transferred across various biological membranes.

Disclosure No potential conflicts of interest relevant to this article were reported.

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