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SPINAL CORD STIMULATION IN CANCER-RELATED PAIN: A REVIEW

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ABSTRACT
Objective: Cancer continues to be one of the global issues as it poses an enormous burden on society in both developed and developing countries. Pain is one of the most common symptoms of cancer affecting millions of people worldwide. This mini-review aims to present the role of spinal cord stimulation (SCS) in treating cancer-related pain. **Method:** Using PubMed, we reviewed the published literature on the use of SCS as a therapeutic strategy for achieving pain relief in cancer patients. **Result:** Eight relevant publications with 96 cancer patients could be retrieved; 4 case reports, one Cochrane review (92 patients), and 4 case series. Despite the significant variability in stimulation protocols, significant pain relief was reported in most of the patients. Complications were rare and minor. **Conclusion:** SCS has emerged out as a promising technique to alleviate chronic cancer-related pain. However, large randomized controlled trials are required to assess the efficacy of this modality and compare it with other standard pain management options.

KEYWORDS: cancer, chronic pain, spinal cord stimulation, neuromodulation.

INTRODUCTION
Cancer continues to be one of the most important medical issues around the globe one of the global issues as it possesses an enormous burden on society in both developed and developing countries. The occurrence of cancer is increasing because of the growth and aging of the population, the increasing prevalence of established risk factors such as smoking, overweight, physical inactivity, and changing reproductive patterns associated with urbanization and economic development. The Global Cancer Observatory estimated about 14.1 million new cases and 8.2 million deaths due to cancer worldwide in 2012 alone.[1]

Pain is one of the most common symptoms of cancer and each year around 9 million cancer patients are affected by it, deteriorating their quality of life.[2] Seventy-five percent of these patients belong in the terminal stages of cancer.[3] Cancer-related pain varies in its type ranging from a constant hot and burning, aching or throbbing type to sharp and shooting, stabbing type of pain over the affected areas.[4] Overall, more than one-third of patients grade their pain as moderate or severe.[5] There are multiple mechanisms involved in the pathophysiology of pain in cancer. A variety of factors secreted by tumor cells sensitize or may excite the primary afferent neurons through their receptors, causing the pain sensation. Also, the tumor growth entraps and injures the nearby nerves, causing neuropathic pain.[2] It is reported that almost 15 – 40% of cancer-related pain is neuropathic.[4]

Management of pain in cancer patients
Opioids have been and remain the most effective pharmacological modality in the management of cancer-related pain. The intensity of pain in these patients increases with time requiring an increasing dose of narcotics or addition of other analgesics which leads to the build-up of deleterious side-effects.[6] Given the failure to find promising new types of analgesics and the growing concern over chronic opioid therapy, the paradigm is shifting slightly away towards the non-pharmacological treatment as an alternative to the fourth step in the ladder of World Health Organization for the management of pain in cancer patients.[7]

Interventional treatment modalities that have been tried in several types of cancer pain range from selective nerve root or zygapophyseal joint block, nerve destruction with radiofrequency or neurolytic agents, to destructive procedures like neurectomy, sympathectomy, and

rhizotomy, and the use of neuromodulation with Spinal Cord Stimulation (SCS).[7,8] Ablative procedures like spinothalamic cordotomy, dorsal root entry zone surgery, midline myelotomy have been done along with neuroaugmentative procedures like deep brain stimulation (DBS), cortical stimulation (MCS) and SCS.[6]

General aspects of Spinal Cord Stimulation

Neuromodulation with SCS is appearing as a promising field in the surgical management of pain in cancer patients not managed with medications alone. Compared to the conventional SCS, new methods like high-frequency SCS, burst SCS, and Dorsal Root Ganglion (DRG) stimulation has been in use more frequently with better results.[9]

Food and Drug Administration has approved the use of SCS for failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), chronic peripheral plexopathy, and neuropathic pain.[10,11] SCS is also being used in other conditions such as peripheral vascular disease, headache, angina pectoris and coronary artery disease.[12]

There are multiple theories regarding the mechanism of action of spinal cord stimulation, the most popular one being the "gate-control theory" of pain as proposed in 1965 by Melzack and Wall which postulates that SCS stimulates and activates the larger myelinated afferent fibers of the dorsal column. This inhibits the transmission of pain to the brain cortex through the spinothalamic tract. This was termed as "dorsal column stimulation" previously but nowadays has evolved to spinal cord stimulation (or even "dorsal horn stimulation") with improved efficacy.[7,13] The placement of SCS electrode leads thus depends on the region of the body where analgesia is needed. Stimulation of C1-2 for the facial pain, down to T7 for the abdominal or T8-9 and down for low back and radicular pain is done for patients with pain complaints in the respective region.[4]

SCS IN CANCER PAIN

Interestingly, the first SCS procedures ever done were in two patients suffering from pelvic and bronchogenic carcinoma. The pain in these patients reduced significantly until the end of their lives. However, this method did not become popular for the treatment of cancer pain because of poor patient selection, technical problems with the implantation, and an ever-changing device design.[10] Thus, there is paucity in the number of published studies supporting the benefit of SCS in cancer-related pain as only a handful of case series and case reports are available (Table 1).[14,15]

Table 1: The available literature on spinal cord stimulation and cancer-related pain.

Authors	Year	Study Type	Total patients	Patients with cancer	Stimulation Parameters	Outcome
Meglio *et al.*[16]	1989	Case series	109	11	85Hz; 210µsec; cycled mode (64 seconds on, 1-4 minutes off)	3/11 received a permanent implantable system. 1/3 reported no effect within 1 month. The other 2 reported 50% pain reduction until death
Shimoji *et.al.*[17]	1993	Case series	454	52	1.6-8Hz; 0.5-5V	29/34 males & 16/18 females achieved significant pain relief of more than 50%.
Cata *et. al.*[19]	2004	Case report	2	2	22Hz; 286µsec; 0–2V; cycles with time on (15 sec) & time off (15 sec)	Negligible pain at 96 hours post-surgery and mild pain (VAS 2/10) at four months post-surgery.
					80Hz; 500µsec; 0–4V	Patient had reduction in his pain score immediately post SCS and after three months.
Tsuboa *et. al.*[21]	2009	Case report	1	1	Lead 1 (T7-T8): 40Hz; 290µsec; 2.6mA Lead 2 (T9-T10): 40Hz; 470µsec; 4.1mA	At 8 weeks post procedure, pain reduced by 30%, significant pain relief at 6 weeks post op.
Yakovlev *et. al.*[22]	2010	Case series	14	14	50-60Hz; 400 - 450ms; 1.5–2.3V	Each patient reported a 100% pain reduction after initial programming. More than 50% of pain reduction was achieved in all patients at 12 months follow-up.
Nouri *et.al.*[20]	2011	Case report	1	1	20Hz; 300µsec	VAS 1/10 without analgetics, until death
Yakovlev *et. al.*[4]	2012	Case series	15	15	40-60Hz; 390-480 ms; 1.4-5.2V	80% pain reduction in all patients immediately postop.; 50% pain reduction in all patients at 12 months FU
Peng *et. al.*[18]	2015	Cochrane review	92 (in four case series)	92	-	VAS among patients decreased significantly post SCS.

Meglio et al. conducted back in 1989 a study with 109 patients with chronic pain treated with SCS. Out of 109, 11 were cancer pain patients. In this study, only 3 of these 11 patients got satisfactory pain relief and received a permanent implantable pulse generator (IPG). One of these three reported no therapeutic effect within one month of permanent stimulation. The other two reported having their pain reduced by half until their death. Compared to the other indications like vasculopathic pain, low back pain, paraplegic pain, and post-herpetic pain, the treatment of patients with cancer pain was less successful. The authors recommended using opiates for cancer pain and not SCS.[16]

In contrast to their findings, Shimoji et al. found that the pain relief (defined as a reduction of more than 50%) was significantly higher in patients with carcinoma and sarcoma compared to the other causes of chronic pain.[17] They used a continuous lower frequency of stimulation (1.6-8Hz) whereas high frequency was used by Meglio et al. (85Hz). The evaluation was done by pain relief scores (subjective) and change in the amount of pain killers post-procedure.

Peng et al., in 2015, in their Cochrane review (updated version), found a paucity of publications regarding the use of SCS in cancer-related pain. No randomized controlled trials were comparing SCS with other interventional modalities. In two articles, the score on the visual analogue scale (VAS) among patients decreased significantly post SCS.[18]

Cata et al., in their case report, presented two patients with chemotherapy-induced pain who underwent SCS. The first patient was a case of Ewing sarcoma with melanoma in his right elbow who developed bilateral lower limb pain after chemotherapy (max. VAS 9.3/10). After a successful trial and implantation of permanent dual leads centered at L1, the patient had negligible pain at 96 hours post-surgery and mild pain (VAS 2/10) at four months post-surgery. His opioid analgesics decreased from 150mg to 30mg/day. The second patient was a case of Ewing sarcoma as well as with lower limb pain post-chemotherapy (max. VAS: 8.8/10). This patient also had a reduction in his pain score immediately post-SCS (VAS 0-2.4/10) and after three months (VAS 3/10). His opioid analgesics were also reduced from 550mg to 480mg/day.[19]

Nouri et al. reported a case of a 57-year-old man who underwent prostatectomy for prostate cancer and presented burning and stabbing pain over his left scrotal and inguinal region. He underwent SCS with dual leads over the T10-T11 dorsal column. His pain remained at 1/10 thereafter and the patient was weaned off from all the analgesics he was taking previously.[20] In another case report of a 76-year-old man with a diagnosis of renal cell carcinoma with invasion of the sacrum and bilateral lower limb pain, SCS was done and the patient achieved a significant pain relief for the next 6 months until death.[21]

Yakovlev et al. reported on fourteen patients with lung cancer who underwent thoracotomy with lung resection. After post-op radiotherapy, they underwent SCS. After the successful SCS trial through temporary percutaneous leads because of thoracic pain, at the T3-T5 level, the patients underwent implantation of permanent leads and IPGs that were programmed with the following parameters: pulse width of 400 - 450 ms; rate of 50-60 Hz; amplitude ranged from 1.5–2.3V. Each patient reported a 100% reduction in pain after initial programming. More than 50% of pain reduction was achieved in all of these patients at 12 months follow-up.[22]

Similarly, in a series of patients by the same author, all 15 patients with low back pain related to cancer who had an SCS trial with percutaneous placement of temporary leads initially for at least two days, reported more than 50% reduction in pain severity. They underwent permanent placement of leads (placed at T8-T10) with rechargeable IPGs two to four weeks later and were programmed with a pulse width of 390 - 480 ms; rate of 40-60 Hz and amplitude ranging from 1.4-5.2V. Initially, each patient reported an 80% pain reduction. At 12 months follow up, a pain reduction of more than 50% was observed in all of the patients.[4]

Complications of SCS

SCS leads were initially placed subdurally but later in the epidural space to minimize the complex nature of the surgery and the postoperative complications. The complications of SCS are the same for all indications and include infections, hematoma formation, neurological injury, pain at the site of the electrode or the IPG, cerebrospinal fluid leakage, and chronic fibrosis.[13,18,23] According to a review with 59 cancer pain patients, the infection rate among those who underwent SCS was 2.7% compared to 3.3% for other non-cancer patients. All of these infections were at the IPG pocket site.[24]

Other complications are lead fracture or disconnection (5%-9%), lead migration (0%-27%), and IPG failure (1.7%). To minimize this, a 3-month limitation of excessive movement of patients allows the leads to get fixed into the implanted side due to postoperative scarring.[13]

CONCLUSION

SCS has emerged as a promising technique to alleviate chronic pain including cancer-related pain in patients who are suffering from intractable pain refractory to pharmacological treatments. Large randomized controlled trials are required to scientifically assess the efficacy of SCS and compare it with other standard pain management alternatives. With its use as an out-patient procedure and with relatively fewer side effects, it would

not come as a surprise if this becomes the new norm for medicine refractory cancer-related pain.

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