

A Case Report

A Case of Spinal Cord Stimulation in Raynaud's Phenomenon: Can Subthreshold Sensory Stimulation Have an Effect?

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Spinal cord stimulation is currently used to treat a variety of chronic intractable painful conditions. We report a case of severe Raynaud's phenomenon in the hands refractory to conservative treatment and responsive to diagnostic stellate ganglion block that was effectively treated with a spinal cord stimulator placed in the cervical epidural space. After capturing the affected areas with paresthesias, blood flow in the left hand and fingers significantly improved as evidenced by an increase in skin temperature, a change from cyanotic to pink appearance and concomitant reduction in pain. Moreover, the patient reported that limb ischemia and pain could be managed overnight with stimulation intensities that were below sensory perception thresholds. Thus it seems, at least in the overnight period, paresthesias were not required to maintain pain relief. This case presents a potential divergence between a requirement for paresthesias and pain relief in spinal cord stimulation therapy for the treatment of Raynaud's phenomenon. The possible role of the sympathetic nervous system in this relationship is also discussed.

Key words: spinal cord stimulator, Raynaud's phenomenon, sensory perception.

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The successful treatment of peripheral neuropathies and vascular disorders with electrical neuromodulation is a growing indication for these types of medical devices (1,2). Although very few high quality clinical trials have been published examining the efficacy of electrical spinal neuromodulation, case reports and case series

indicate varying success rates in treating these painful conditions (1,2). One such condition is Raynaud's phenomenon. First described by Maurice Raynaud (3), this condition results from an exaggerated, episodic, and reversible vasospastic reduction in blood flow to the fingers and the toes (4,5). Classically this condition is induced by cold or emotional responses.

The digits feel cold to the touch, typically have a pallor appearance, and bouts of ischemia lead to a cyanotic appearance accompanied by severe pain (4, 6). Measurements of blood flow and tissue oxygenation are typically reduced. The effects are observed more often in the upper extremities versus the lower extremities and more often in females than males with approximately a 2:1 ratio (7). The exact etiology and underlying pathophysiology of Raynaud's phenomenon is unclear (8-10).

Prior case reports have demonstrated the effects of spinal cord stimulation on peripheral blood flow, oxygenation, and pain levels in severe cases of Raynaud's syndrome (11-14). We present an interesting case of severe Raynaud's phenomenon that was very effectively treated with a spinal cord stimulator, even at stimulation intensities below sensory threshold. This is in direct contrast to prior work suggesting that paresthesias are a requirement for pain relief and may be related to the effects on sympathetic nerve outflow (15).

CASE PRESENTATION

History

A 53-year-old Caucasian female with a previous medical history of hypertension, renal insufficiency, and hypertrophic cardiomyopathy was referred to the pain center for evaluation and management of chronic bilateral pain in her hands, and in particular her left hand which was diagnosed with Raynaud's phenomenon. Previous surgeries included thyroidectomy and parathyroidectomy, nephrectomy and adrenal resection for pheochromocytoma, and 2 lumbar decompression laminectomies. In general, the digits on her left hand were cold to touch with a white or cyanotic appearance and poor capillary refill (Fig. 1). Specifically, the patient's left proximal, middle phalanx had a whitish appearance while the more distal portion had a cyanotic discoloration, superficial lesion, and associated pain. The distal portion of the left index finger up to the second knuckle was amputated due to ischemic induced necrosis. Photoplethysmographic diagnostic testing yielded abnormal blood flows in 3 out of 5 digits. The blood flow measurements in the brachial, radial, and ulnar regions were normal thus excluding a proximal blockage (taken at a different clinic). The patient described burning and throbbing pain levels as at best a 5 and at worst a 10 (on a scale of 0 to 10, with 0 being pain-free and 10 being the

worst pain imaginable); touch allodynia in the affected digits was also noted. Based upon the examination and presentation it is possible that the Raynaud's was secondary to other disease processes (i.e. pheochromocytoma) and not a primary Raynaud's phenomenon (5). Peripheral neuropathic pain was diagnosed in the right hand, and therefore the left hand may have had a mixed pain component comprised of ischemia and neuropathy. The patient was intolerant to many common analgesics (including opioids and non-steroidal anti-inflammatory drugs) and, therefore, was unable to pharmacologically control the pain in her left hand. She indicated that she was taking acetaminophen but this provided minimal relief. The patient was also taking hydrochlorothiazide and lisinopril (to treat her hypertension and cardiomyopathy), levothyroxine to treat hypothyroidism, and calcitrol to help control post-surgical hypoparathyroidism.

Treatment

Following failure of conservative therapy the first interventional procedure was a diagnostic left Stellate Ganglion block (.25% Marcaine mixed with 1% Lidocaine) providing 90% relief of pain in the left hand for approximately 3 hours. Following the first Stellate Ganglion blockade, skin temperature on the dorsal surface of the hand increased 2°C. A second left Stellate Ganglion block provided 80% relief for 2 hours, validating the diagnostic effect and also providing evidence of a sympathetically mediated pain in the left hand. At this point the patient was informed about spinal cord stimulation therapy and she decided to proceed with the device trial.

Following dual trial lead placement at C4 (2 Compact Octad Trial Leads, Medtronic, Minneapolis, MN) and initial programming that captured the fingers, hands, and arms, the surface skin temperature almost immediately increased in the patient's left hand and fingers (patient reported and subjectively observed). The digits turned pink and were warm to the touch. A two lead configuration was utilized to maximize the potential of capturing distal portions of both hands. The patient was given 2 programs to utilize following implantation; the frequency used was 60 Hz, pulse width varied from 360 to 390 μ s and voltage ranged from 2.1 to 2.8 (constant voltage system – current was not measured). At the end of the 8 day trial we could obtain a pulse oximetry waveform from the left, middle digit; this could not be obtained on the day of the trial. The latter suggests that blood flow had increased

to the fingers; however, we did not have equipment to verify this with other more sensitive techniques. The patient indicated that she received >80% pain relief for the duration of the trial and decided to proceed with the implantation phase. The patient was implanted with a spinal cord stimulation system (2 Octad leads connected to a RestorePRIME™ Generator, Medtronic, Minneapolis, MN) and reports excellent relief up to 6 months following implantation. Similar programming was performed as during the trial.

During a routine follow-up phone call we inquired about the usage of the device. The patient indicated that she used the device quite a bit, however in the evenings she would turn the device waveform amplitude down below sensory threshold (i.e. could not feel paresthesia; it is unknown what the voltage was during the subthreshold stimulation) while still maintaining excellent relief. The patient also indicated that this was the case throughout an entire evening of sleep (approximately 6 – 8 hours). During



Fig. 1. Upper Panels. Lateral (left panel) and anterioposterior (right panel) fluoroscopic images of dual Octad lead placement. Lead tips were positioned at C4 and the arms and hands were captured bilaterally. Although the leads appear to be touching, functionally they were not (no electrical short). Lower Panels. Prior to spinal cord stimulator trial fingers were cyanotic. Note the superficial ulceration on the extremely cyanotic middle digit and general pallor. Almost immediately following initiation of the trial the hand and fingers were warm and pink; picture on the right indicates condition of the hand following 8 trial days. This patient already had the distal portion of the index finger amputated due to ischemic necrosis prior to trialing the spinal cord stimulator.

the interim period between the trial and implant the patient indicated that the pain had returned suggesting that when stimulation was not present at all painful ischemic conditions returned.

Discussion

The current case report highlights the effectiveness of treating Raynaud's phenomenon with spinal cord stimulation therapy. To date there have been no randomized, prospectively designed studies to determine the efficacy of neuromodulation in the treatment of this painful disorder. Rather, there are scant few cases published with similar positive outcomes (11-14,16).

This case is interesting because it highlights several different potential mechanistic aspects of spinal cord stimulation. The repeatedly successful stellate ganglion blocks indicate that the ischemia and resultant pain in the left hand were, at least partially, sympathetically mediated. Palliative treatment of the pain with various pharmacological agents was ineffective; but it is important to remember that these drugs would still have not helped increase peripheral blood flow and, theoretically, digit survivability. The qualitative increase in left digit blood flow suggests that the spinal cord stimulator was reducing sympathetic flow to the peripheral vasculature. Ideally, we would have measured blood flow utilizing a plethysmographic technique; however, our center was not equipped to take those measurements at the time. Clearly, future clinical trials will need to measure blood flow, and potentially sympathetic nerve outflow, to help provide a mechanistic understanding of SCS therapy in Raynaud's cases.

Similar mechanisms have been documented in animals although the neural mechanism(s) by which this reduction in sympathetic nerve outflow occurs is unknown (17). Interestingly, retrograde tracing with viral vectors injected into rat stellate ganglion labels cells in the superficial dorsal horn, suggesting that cells in this region of the spinal cord project to the intermediolateral cell column and eventually to sympathetically innervated peripheral tissues (18). Thus, a functional connection between sensory neurons in the dorsal horn and sympathetic pre-ganglionic neurons in the spinal cord could provide a mechanism by which spinal cord stimulators provide a sympatholytic effect resulting in an increase in peripheral blood flow.

Naver et al reported a case in which a patient underwent unilateral sympathectomy after which spinal

cord stimulation increased peripheral blood flow only on the sympathetically intact side and not the sympathetically denervated side (19). This case suggests a critical role for sympathetic fibers mediating SCS-evoked increases in blood flow. Also, efferent sympathetic outflow may be dependent upon spinal lead placement. One study found increased catecholamines following spinal cord stimulation when leads were placed at T5-7 (20). While it is not surprising that blood pressure remained fairly constant due to arterial baroreceptor reflexes, these data suggest that sympathetic outflow might have been increased to the adrenal glands or there was increased "spillover" from sympathetic nerve terminals into the circulation. These findings are in direct contrast to those demonstrating increases in blood flow (and presumably decreases in sympathetic flow) in the upper and lower extremities (21-24). The importance of sympathetic outflow in the long-term treatment of Raynaud's is controversial. In a case series of 140 patients, de Trafford and colleagues found that less than 20% of the patients benefited from the procedure at a 1 year follow-up despite very good relief in the shorter term (25). These data question how much of a role sympathetic nerve regulation plays in the management of Raynaud's associated pain. It is most likely the case that different pathophysiologic conditions, including abnormal sympathetic regulation, produce a Raynaud's phenomenon and these mechanisms might differ between patients (26). In the present case, abnormal adrenergic receptor function following the resolution of pheochromocytoma may have played some role in the ischemic bouts.

In the current case, it seems that altered sympathetic nerve outflow was ameliorated with spinal cord stimulation, thereby increasing blood flow to the periphery and alleviating pain. In fact, Hord and colleagues demonstrated patients that responded to sympathetic nerve blocks were more likely to have positive outcomes to spinal cord stimulation (27). However, other studies have suggested that peripheral vasodilatation is not necessarily a requisite for pain relief in all conditions (28). Rather, it is more likely that spinal cord stimulation activates or inhibits a variety of neural pathways and mechanisms that, in concert, produce analgesia (29,30). Our case also does not directly address mechanisms by which SCS may relieve pain in ischemic conditions such as Raynaud's phenomenon. Specifically, it is unclear if the observed Raynaud's phenomenon is a sympathetically maintained or a sympathetically mediated condition. Moreover, it

is unclear if other peripheral mechanisms might have contributed to this condition. Spinal cord stimulation therapy seems to be effective in other painful conditions that putatively involve the sympathetic nervous system (e.g. CRPS). This suggests that there may be some therapeutic benefit in conditions that involve either the afferent or efferent sympathetic nerve fibers. In future clinical studies, identifying painful conditions as sympathetically maintained versus mediated may help to more clearly define the therapeutic application and utility of spinal cord stimulation.

It is interesting to note that in the patient presented in this case, painful ischemic bouts were adequately controlled when stimulation intensity was turned below stimulation intensities that generated paresthesias (i.e. sensory threshold). Anecdotally, we have noticed that pain relief continues for approximately 30 minutes following stimulation cessation, perhaps due to residual neuromodulatory effects. Previous studies have documented rebound pain with discontinued use of spinal cord stimulators (31,32); however we did not find any study that assessed the effectiveness of brief or longer-term subthreshold stimula-

tion. Presumably the paresthesia that is produced by dorsal column stimulation is through activation of Aβ fibers impinging on cells in the dorsal horn (33,34). Since stimulation effectiveness was maintained during a time period where we would anticipate rebound pain to present, there seems to be a divergence in the mechanisms underlying the paresthesia and reductions in sympathetic nerve outflow and increases in blood flow. At present, the reason for this potential divergence is unclear.

In conclusion, spinal cord stimulation therapy is an option for treating severe Raynaud's phenomenon that is refractory to other conservative therapeutic options even at subthreshold stimulation intensities. It is not clear how long subthreshold stimulation can maintain pain relief; however, in the current case relief was maintained overnight. Controlled trials, direct measurements of sympathetic outflow, and mechanistic studies are needed to more fully describe the apparent disparity between perceived sensory stimulation and autonomic outflow observed in this case, as well as to assess the long-term efficacy, amputation rates, and cost-effectiveness.

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