

Pain Relief and Functional Recovery in Patients with Complex Regional Pain Syndrome after Motor Cortex Stimulation

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Key Words

Complex regional pain syndrome • Motor cortex stimulation • Positron emission tomography • Spinal cord stimulation

Abstract

In addition to pain and neurovegetative symptoms, patients with severe forms of complex regional pain syndrome (CRPS) develop a broad range of symptoms, including sensory disturbances, motor impairment and dystonic posturing. While most patients respond to medical therapy, some are considered refractory and become surgical candidates. To date, the most commonly used surgical procedure for CRPS has been spinal cord stimulation. This therapy often leads to important analgesic effects, but no sensory or motor improvements. We report on 2 patients with pain related to CRPS and severe functional deficits treated with motor cortex stimulation (MCS) who not only had significant analgesic effects, but also improvements in sensory and motor symptoms. In the long term (27 and 36 months after surgery), visual analog scale pain scores were improved by 60–70% as compared to baseline. There was also a significant increase in the range of

motion in the joints of the affected limbs and an improvement in allodynia, hyperpathia and hypoesthesia. Positron emission tomography scan in both subjects revealed that MCS influenced regions involved in the circuitry of pain.

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Introduction

Complex regional pain syndrome (CRPS) is a condition associated with chronic pain and neurovegetative changes of the affected limbs [1]. In severe cases, the spectrum of symptoms is often broad and includes sensory disturbances, tactile, thermal and pain anesthesia, progressive motor impairment and dystonic posturing [2–4]. Though most patients respond to medications and physiotherapy, some are considered to be refractory. For this population, surgery often represents an important therapeutic option. To date, the most commonly used surgical intervention to treat patients with CRPS has been spinal cord stimulation (SCS). Though this surgical modality is associated with important analgesic effects, sensory and motor symptoms often do not improve to the same ex-

tent. Only a few studies have specifically used motor cortex stimulation (MCS) to treat patients with CRPS [5].

We report on 2 CRPS patients who had only transient benefit with SCS and were subsequently treated with MCS. After surgery, both subjects presented not only significant pain relief but also an improvement in sensory and motor symptoms.

Methods

Patients

Patient 1 was a 32-year-old man with a 5-year history of a minor traumatic injury to the third finger of his left hand (cut with a sharp instrument). Two weeks after the accident, he developed a hot-burning, stabbing and sharp pain that soon became resistant to over-the-counter analgesics. Within 2 months, the pain compromised the whole forearm and distal portion of the arm with no radicular distribution. At that time, neurovegetative and trophic changes were first noticed in his hand and fingers. With the progression of the disease, he developed a fixed dystonic posture with flexion of the fingers, wrist, and elbow, preventing him from moving the affected hand [6]. Associated with the severe pain [visual analog scale (VAS) score = 10], tactile hypoesthesia, allodynia and hyperalgesia were noticed over the fingers and hand. At that point, an area of tactile, thermal, and proprioceptive hypo/anesthesia was clearly noticed in his fingers and hand. Treatment with tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, neuroleptics, anticonvulsants, oral baclofen, benzodiazepines, and opioids in adequate doses was of limited efficacy. The patient was also treated with physical therapy, acupuncture, sympathetic blocks and a brachial plexus block, all with unsatisfactory results. He then underwent SCS. This was conducted through a 4-contact electrode implanted at the level of C6–C7. Stimulation-induced paresthesias covering the whole painful region were elicited with the following parameters: 1.7–3.8 V, 210 μ s, 50 Hz. Overall, a 60% reduction in pain scores was recorded with substantial improvements in allodynia and hyperalgesia. No effects were noticed on motor or sensory deficits. Fourteen months later, the analgesic effects of SCS were lost (though the patient continued to experience stimulation-induced paresthesias in the painful regions of his upper limb). Impedance was confirmed to be in the normal range and displacement of the electrode was ruled out with imaging studies. Intensive reprogramming did not provide the initial analgesic results. The patient was then offered MCS.

Patient 2 was a 26-year-old man with a 4-year history of right upper limb pain following a traumatic injury to the tip of his index finger (pressed between doors of an elevator). Fractures were ruled out at the time of the accident. Three weeks after the accident, he developed a burning, stinging pain in his right index finger, which soon compromised the entire hand, forearm and distal portion of the arm. Trophic and neurovegetative changes were noticed initially in his hand, but also forearm. Allodynia and hyperalgesia were present in the whole right upper extremity, whereas a decrease in tactile and thermal sensation was noticed in the hand. Two months later, the patient developed a progressive fixed dystonic posture, with flexion of his fingers and

elbow and extension of the wrist. He was subsequently referred to our clinic for pain management, where he received tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, anti-convulsants, oral baclofen, benzodiazepines, and opioids, with no significant benefit. Physical therapy, acupuncture, guanethidine injections and a stellate ganglion block were also attempted with no satisfactory results. As with patient 1, an area of tactile, thermal, and proprioceptive hypo/anesthesia in the fingers and hand was noticed with progression of the disease. While he reported an unbearable pain in his whole upper limb, he also had the subjective impression that the distal portion of his forearm and hand did not exist. This phenomenon was described in his own words as follows: 'Although I can see my forearm and hand, when I close my eyes I do not feel them as part of my body.' Similar to patient 1, SCS led to a 50% reduction in VAS scores but no changes in motor or sensory deficits. Twelve months later, the analgesic effects of stimulation were lost and the patient was offered MCS.

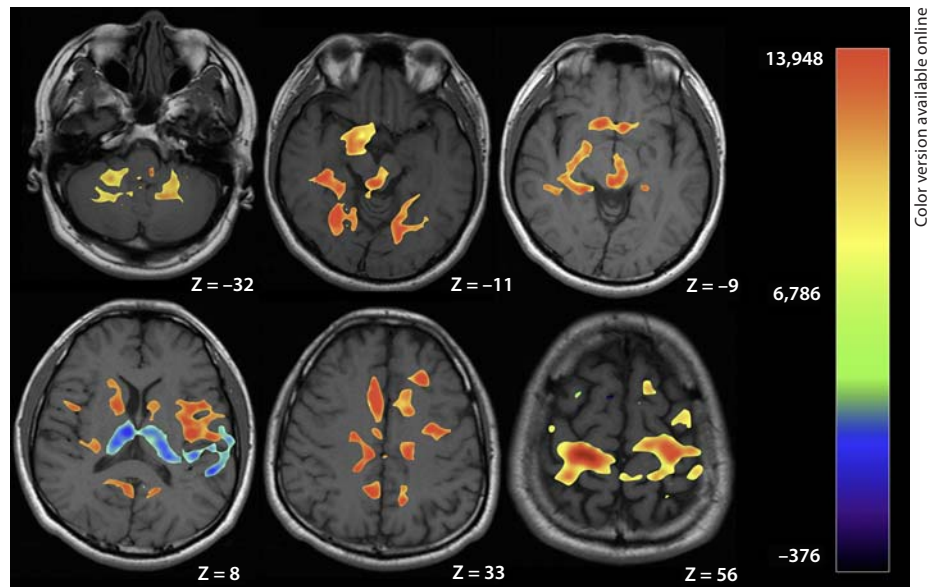
Surgical Procedure

The best approach to determine the site for implanting MCS electrodes is still a matter of debate. We rely on anatomical MRI localization [7], transcranial magnetic stimulation and intraoperative epidural stimulation.

MR images were obtained a few days before surgery and used to assess the tentative anatomical target (i.e. hand knob on axial images) [7, 8]. Preoperative transcranial magnetic stimulation (MagProX100, MagVenture, Denmark) was conducted to map the regions from which contractions of the first interosseous muscle could be induced at 120% of the resting motor threshold.

On the morning of the surgery, a stereotactic frame (TM Micromar, São Paulo, Brazil) was placed under local anesthesia and a CT scan was obtained. Stereotactic CT and T₁-weighted MR images were fused (Stereotactic Assistant Software, Micromar, Brazil) and the coordinates of the hand knob area were calculated [7]. A small craniotomy (3 cm) encompassing the region of the anatomical target and the area mapped with transcranial magnetic stimulation was then carried out under local anesthesia and light sedation. Bipolar stimulation of the epidural space was conducted with pulses of up to 4 mA, 1 ms and 30 Hz (Micromar AC Cortical Stimulator, São Paulo, Brazil). Once mapping was finished, an epidural paddle electrode (Resume II, model 3587A, Medtronic, Minneapolis, Minn., USA) was implanted perpendicular to the central sulcus over the area of the greatest evoked motor responses. At the end, two electrode contacts were placed over the precentral and two over the postcentral gyri contralateral to the patients' pain. Precentral (0 or 1) and postcentral contacts (2 or 3) were tested as cathodes and anodes, respectively.

In both subjects, programming was started 1 day after the insertion of the electrodes and continued for 2 weeks, while patients were still in the hospital. Monopolar and bipolar settings were tested at different frequencies (10, 30, 60 and 100 Hz) and pulse widths (90–210 μ s). Intensity was always kept under 80% of the motor threshold in patient 1 and under 80% of the threshold to evoke a sensation of movement in patient 2. Stimulation at 3–5 V, 120–210 μ s, and 10–25 Hz with a bipolar configuration (contact 1–2+) was associated with a \geq 50% reduction in VAS scores as compared to the 'off' stimulation condition. As a result, patients



Color version available online

Fig. 1. Results of regional brain activation- (FDG-PET) related findings after voxel-based image subtraction (Matlab®/ImageJ software), fused onto the MRI (Osirix® software) and plotted into the Talarach Atlas (Brainsight® software). The plates represent the subtraction of images in ‘on’ and ‘off’ stimulation conditions in CRPS patients treated with low-frequency stimulation of the motor cortex. The color scale bar on the right shows areas with a significant increase in metabolic activation during stimulation (red and yellow) as well as a decrease (blue and green; for colors,

see online version). Increased activity during stimulation was observed in the cingulate cortex and precentral gyri (bilaterally), right posterior insula, bilateral inferior medial temporal cortex, bilateral nucleus accubens and the mesencephalic region (periaqueductal gray). In addition, a decreased activity has been observed in the thalamus bilaterally. At the bottom, ‘Z’ values show the brain slice distance from the AC-PC line (coordinates of the Talarach Atlas).

underwent the placement of pulse generators (IPG; Itrel III, model 7425, Medtronic Inc.), being discharged on the following day. The first programming session was carried out 1 week later.

Positron Emission Tomography

Positron emission tomography (PET) studies in the ‘on’ or ‘off’ stimulation conditions were performed on 2 consecutive days 6 months after surgery (Allegro PET scanner; Philips Medical Systems). Off stimulation scans were acquired 10–12 h after the electrodes were turned off. The time course of fluorodeoxyglucose (FDG) radioactivity was obtained by repetitive sampling images of the brain for 40 min after the administration of FDG. Three-dimensional parametric images representing regional cerebral metabolic rate of glucose were then calculated. For spatial normalization, images were transformed into the MNI-152 (Montreal Neurological Institute) template. An isotropic Gaussian kernel of 10 mm full width at half maximum was applied to improve the signal-to-noise ratio. Finally, spatially normalized and smoothed regional cerebral metabolic rate of glucose images were analyzed in order to prompt positive (on – off) and negative (off – on) results, through the subtraction of voxel intensities. Voxel intensity normalization, realignment, and volumetric subtraction were performed using the Osirix® and ImageJ® software. The images are presented as the average of the results of volumetric subtraction fused to the MR images (fig. 1).

Results

Both subjects in our study had a long-lasting analgesic effect after MCS (contacts 1–2+, 3 V, 210 μ s, 10 Hz). In patients 1 and 2, improvement at 6 months and at the last follow-up (27 and 36 months after surgery) was in the order of 60–70% as compared to baseline (VAS scores of 3 and 4). Medication intake was significantly reduced in both individuals, who continued to be treated with physiotherapy. It is worth mentioning, however, that neither physiotherapy alone nor combined with medications or SCS provided a significant improvement during the 4–5 years preceding MCS.

Of interest, patient 1 had his electrode accidentally turned off, returning to the clinic due to pain recurrence. Soon after the electrodes were turned on again, the benefits of stimulation were recaptured.

Aside from the analgesic effects of MCS, a striking feature in our study was the motor and sensory improvement observed in both patients. During the last follow-up assessment, patient 1 still reported mild allodynia, hyper-

Table 1. Outcome of MCS in patients with CRPS

	Patient 1		Patient 2	
	preoperative	postoperative	preoperative	postoperative
VAS scores	9	3	10	4
McGill scores	69	32	72	28
Regions of allodynia/hyperpathia	hand forearm	fingers	hand forearm	hand fingers
Range of active motion of the joints, degrees	distal arm fingers 0 wrist 0 elbow 0	40 60 120	distal arm fingers 0 wrist ¹ elbow 0	60 100
Distorted body scheme	–		hand forearm arm	hand fingers
Follow-up, months	27		36	
Stimulation parameters	1–2+, 3 V, 210 μ s, 10 Hz		1–2+, 3.6 V, 210 μ s, 10 Hz	
Individual FDG-PET during stimulation	– Reduced activity bilaterally in the thalamus – Significantly increased activity in the region of the motor cortex adjacent to the electrode and in the mesencephalon, cingulate cortex, nucleus accubens, posterior medial temporal cortex, cerebellum and insula		– Reduced activity bilaterally in the thalamus and posterior insula – Increased activity in the region of the motor cortex (bilaterally), nucleus accubens, posterior medial temporal cortex, cerebellum and in the periaqueductal region of the mesencephalon	

¹ This patient had an orthopedic fixative procedure and could not move the hand after surgery.

algnesia and tactile hypoesthesia but those were now limited to the tip of his fingers (table 1). Movements in his dystonic arm have also improved. While preoperatively he could not move his wrist and elbow, after 8 months of MCS the range of motion in these joints was 60 and 120°, respectively (table 1).

Patient 2 reported a similar pattern of improvement in allodynia, hyperalgesia, and tactile hypoesthesia (table 1). The range of motion in his elbow went from 0 to 100° after MCS (due to his previous orthopedic procedure we could not assess whether changes occurred in the wrist). Curiously, in addition to these benefits, he also claimed that his phantom phenomenon was improved. In contrast to the preoperative period, he reported being able to feel his arm and forearm (but not the hand) when his eyes were closed after surgery.

To investigate the circuitry modulated by MCS, FDG-PET was carried out with the electrodes turned ‘on’ or ‘off’ 6 months after surgery. As previously reported [7, 9], we found that stimulation was able to influence activity in several areas involved in the circuitry of pain (table 1). In both patients, a bilateral reduced activity was observed

in the thalami, whereas an increased activity has been recorded in the midbrain, cingulate cortex, precentral gyrus and insula. Due to the small number of individuals in our analysis, however, the significance of these findings is difficult to ascertain.

Discussion

Pain control in CRPS is a challenge and has been the subject of investigation in the field of neuromodulation [10]. To date, only a handful of CRPS patients have been reported in a few MCS series. These, however, were often considered under the label ‘chronic neuropathic pain’ with no clear discrimination of outcome being reported [11–13], except for a single series that has specifically studied the effects of MCS on CRPS [5].

We provide a detailed description of 2 patients with CRPS I successfully treated with MCS, who not only had experienced an analgesic effect after stimulation but also had an improvement in sensory and motor symptoms. These results corroborate those of a recent report

by Velasco et al. [5], who demonstrated the efficacy of MCS in 5 patients with CRPS of different etiologies. Four patients showed an important decrease in pain, sensory and sympathetic changes during the therapeutic trial and were implanted with definitive electrodes and pulse generators. One patient did not benefit from the procedure and had the electrode explanted. In patients who responded to MCS, VAS and McGill pain scale scores were significantly reduced throughout the follow-up (though some patients with brachial plexus injury also had dorsal root entry zone lesions). Similar to our 2 patients, improvement in pain scores was associated with amelioration in allodynia, hyperalgesia and sympathetic signs [5]. Features that were also improved in our series and have not been reported in others include a phantom phenomenon and dystonia associated with CRPS. Yet, MCS has been investigated as a therapy in patients with dystonia with promising preliminary reports [14, 15].

Our PET findings suggest that MCS was able to modulate distant brain regions involved in the circuitry of pain, including the thalamus, midbrain, cingulate cortex and insula [16]. Using H₂O PET, Peyron et al. [17] have recently studied cerebral blood flow changes in patients with neuropathic pain undergoing MCS. Three conditions were assessed: before, during and after stimulation. Compared to baseline, MCS was associated with cerebral blood flow increase in midcingulate and dorsolateral prefrontal (BA10) cortical regions. More remarkable changes, however, were recorded when stimulation was discontinued. Under these circumstances, significant differences in cerebral blood flow have been observed in the cingulate gyrus, orbitofrontal cortex, putamen, thalami, prefrontal areas and brainstem, including the midbrain/periaqueductal gray (PAG) and pons [17].

These findings are in agreement with recent studies from our group in an animal model of neuropathic pain [18]. We have recently shown that rats treated with MCS after undergoing constriction of the sciatic nerve had significant metabolic changes in cerebral and spinal cord regions implicated in the pathophysiology of pain. In the dorsal horn of the spinal cord (DHSC) [19], animals treated with MCS had a decrease in Fos and zif expression. This is in agreement with electrophysiological studies showing that MCS inhibits DHSC cells in response to mechanical stimulation [20]. Taken together, these results suggest that the analgesic effects of MCS might be due to the inhibition of DHSC neurons, either through the modulation of cortical-spinal pathways or the descending inhibitory system.

Similar to our patients, rodents with neuropathic pain receiving MCS have an increase in Fos and zif expression in the PAG [19]. This structure is a part of a descending pain suppressor pathway that projects to the DHSC via the rostral ventromedial medulla [21]. These projections comprise an essential part of the neural circuitry for opioid-based antinociception [21]. In humans, MCS has been shown to influence the levels of endogenous opioids in the cingulate gyrus and PAG [16]. Changes in the nociceptive threshold after MCS in rodents also seem to involve the opioid system [18].

The thalamus plays an important role not only as a relay of nociceptive information, but also in the integration of sensory and discriminative components of pain (this later particularly through the ventralposterolateral and ventralposteromedial nuclei) [22]. In rodents with neuropathic pain, we found that MCS induced a significant decrease in Fos and zif expression in the ventralposterolateral and ventralposteromedial nuclei [16, 19]. This could be another mechanism through which MCS may modulate ascending afferent information from the spinal cord in neuropathic pain. Alternatively, MCS may modulate thalamic activity anterogradely or retrogradely through reciprocal corticothalamic projections [23, 24].

The anterior cingulate cortex (ACC) and insula play an important role in mechanisms of pain. Imaging studies in humans have shown insular activation in response to painful stimuli [17]. In patients with epilepsy undergoing stereoecephalographic mapping, painful somatic sensations have been reported during electrical stimulation of the insula [25, 26]. ACC lesions selectively reduce the affective component of neuropathic pain [27], whereas ACC stimulation in rodents inhibits mechanical allodynia [28]. In addition to affective and emotional components of pain, the ACC has also been suggested to induce analgesia through its influence over descending PAG and spinal cord projections.

In summary, we showed in a small number of patients that MCS was not only able to improve pain but also sensory and motor symptoms of severe CRPS. Future controlled studies in a larger number of patients are still needed to establish the role of MCS in the therapeutic armamentarium against CRPS.

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