PAIN® xxx (2009) xxx–xxx

PAIN®

www.elsevier.com/locate/pain

Motor cortex electrical stimulation applied to patients with complex regional pain syndrome

Francisco Velasco [a,*], José D. Carrillo-Ruiz [a,c], Guillermo Castro [a], Carlos Argüelles [a], Ana L. Velasco [a], Alicia Kassian [a], Uriah Guevara [b]

[a] Unit for Stereotactic, Functional Neurosurgery and Radiosurgery of the Service of Neurology and Neurosurgery and Pain Clinic, General Hospital of Mexico, Mexico City, Mexico
[b] Pain Clinic, National Institute of Nutrition and Medical Sciences Salvador Zubirán, Mexico City, Mexico
[c] Psychophysiology and Neuroscience Department, Psychology School, Anahuac University, Mexico City, Mexico

ARTICLE INFO

Article history:
Received 30 March 2009
Received in revised form 2 July 2009
Accepted 18 August 2009
Available online xxxx

Keywords:
Complex regional pain syndrome
Motor cortex electrical stimulation
Induced cutaneous sensory changes
Induced sympathetic changes
Visual analog scale

ABSTRACT

Motor cortex stimulation (MCS) is useful to treat patients with neuropathic pain syndromes, unresponsive to medical treatment. Complex regional pain syndrome (CRPS) is a segmentary disease treated successfully by spinal cord stimulation (SCS). However, CRPS often affects large body segments difficult to cover by SCS. This study analyzed the MCS efficacy in patients with CRPS affecting them. Five patients with CRPS of different etiologies underwent a small craniotomy for unilateral 20-grid-contact implantation on MC, guided by craniometric landmarks. Neurophysiological and clinical tests were performed to identify the contacts position and the best analgesic responses to MCS. The grid was replaced by a definitive 4-contacts-electrode connected to an internalized system. Pain was evaluated by international scales. Changes in sympathetic symptoms, including temperature, perspiration, color and swelling were evaluated. Pre-operative and post-operative monthly evaluations were performed during one year. A double-blind maneuver was introduced assigning two groups. One had stimulators turned OFF from day 30–60 and the other from day 60–90. Four patients showed important decrease in pain, sensory and sympathetic changes during the therapeutic trial, while one patient did not have any improvement and was rejected for implantation. VAS and McGill pain scales diminished significantly ($p < 0.01$) throughout the follow-up, accompanied by disappearance of the sensory (allodynea and hyperalgesia) and sympathetic signs. MCS is effective not only to treat pain, but also improve the sympathetic changes in CPRS. Mechanism of action is actually unclear, but seems to involve sensory input at the level of the spinal cord.

1. Introduction

Complex regional pain syndrome (CRPS) is the term used for describing a variety of pain syndromes initially related with nerve lesions of different etiologies. These syndromes involve mainly distal body segments that present cutaneous sensory changes such as allodynea, spontaneous pain, and hyperalgesia, as well as autonomic abnormalities such as edema, discoloration, changes in temperature, and trophic changes. Typically, the painful area outlasts the territory of the damaged nerve [6,7].

Treatment of CRPS is palliative to date. Pharmacologic management includes analgesics, non-steroid anti-inflammatory drugs (NSAIDS), corticosteroids, and anti-neuritic and *N*-methyl D-aspartate (NMDA) antagonists. Other forms of therapy, such as psychotherapy, physiotherapy, and rehabilitation medicine, have been found helpful. More resistant cases are treated with nerve, sympathetic, or regional blocks and even subarachnoid drug infusion. Neuromodulation has been considered the last step in the CRPS treatment algorithm, for employment when other treatments have failed [17,35,42].

Spinal cord stimulation (SCS) has been reported as successful in the treatment of this syndrome in up to 83% of cases [8]. Pain improvement has been associated with changes in the sympathetic symptoms accompanying CRPS [4,5,25,34,36]. Also, pain relief-associated decreases in allodynea and hyperalgesia have been reported with SCS. However, quantitative evaluation of changes in threshold of different sensory modalities has demonstrated that SCS neither reduces painful sensory symptoms, nor produces decrease in sensitivity in the painful territory [24].

The present report describes a group of cases in which patients fulfilled all CRPS diagnostic criteria according to IASP [7] and treated by motor cortex electrical stimulation (MCS), a different form of neuromodulation that was originally proposed for neuropathic pain of central origin [43–45].

* Corresponding author. Address: Crestón 116, Col. Jardines del Pedregal. 01900 México, D.F., Mexico. Tel./fax: +52 55 51 35 33 61.
E-mail address: slanfe@prodigy.net.mx (F. Velasco).

0304-3959/$36.00 © 2009 Published by Elsevier B.V. on behalf of International Association for the Study of Pain.
doi:10.1016/j.pain.2009.08.024

Theses cases were presented in a previous report (part of the whole group) on the efficacy of MCS in different deafferentation pain syndromes [47]. Nonetheless, the specific effect of MCS on pain severity of CRPS, as well as on condition-related sensory and sympathetic changes, deserves a separate publication. Moreover, during the long-term follow-up of 3–6 years, a number of interesting circumstances such as loss of MCS efficacy require analysis.

Our cases could have been proposed for SCS; nevertheless, in view of the large painful territory that in all cases involved the shoulder, arm, and part of upper chest and neck, we considered that multiple electrodes for SCS would have been necessary to cover the area. In contrast, representation of the entire arm from neck to upper chest in the motor cortex could be covered by a single tetrapolar extradural plate electrode placed over the motor cortex (MC) trajectory between the upper and lower frontal sulci distance [28,46]. There is only one report of MCS for alleviation of pain in CRPS in the literature published in English [40]. In that report, the painful territory extended to the entire hemi-body; thus, the reason for deciding on MCS may have been similar to ours.

Goals establish pain MCS efficacy and sympathetic changes in CPRS patients that included evaluations OFF stimulation performed in a double-blind protocol.

2. Patients and methods

Five patients with complex regional pain syndrome (CRPS) were considered for MCS. Table 1 summarizes their clinical characteristics. There were four females and one male with an age range from 29 to 79 years (mean, 47.6 years) and a history of CRPS from 1.5 to 15 years (mean, 5.1 years). Etiology in three cases was trauma in the brachial plexus (avulsion): one patient with complete motor and sensory function lost in shoulder and arm, another with paresis and muscular atrophy of shoulder and arm and complete paralysis of C5–C6 innervated muscles, and a third patient, without motor deficit. One patient suffered from a rare multiple arteriovenous shunt malformation in left arm, shoulder, and chest diagnosed as hemangiectasy (Parkes–Weber syndrome) [48], and another patient had a 15-year history of scleroderma and neuropathy associated with her primary disease [37], in this patient, motor dysfunction was difficult to evaluate because of deformities in joints, and the cutaneous and muscular stigmas of the disease. All patients had swelling, discoloration, perspiration, and temperature changes in the painful territory. Additionally, all patients had areas of hyperalgesia and allodynea, and in two of them areas of painful anesthesia. Previous treatments for CRPS included multiple forms of analgesics, sympathetic blocks, and peripheral nerve blocks, plus specific treatments for the disease such as open and endovascular occlusion of arterial venous malformations. Despite these treatments, patients ranked pain intensity repeatedly as maximal or extreme, and were totally incapacitated due to pain.

The protocol of study was revised and approved by the Ethical Committee of our institution. Participating patients signed an informed consent that complied with Helsinki declaration regulations.

Under general anesthesia, a craniotomy was performed centered over the Rolando fissure to place a extradural 4 × 5-cm 20-contact grid (Ad-Tech Instruments, Racine WI, USA). The position of the motor cortex (MC), its trajectory, and the cortical representation of the painful territory were defined using imaging, and when it possible somatic evoked responses to median nerve stimulation, and low- and high-frequency cortical-cortical evoked responses induced by bipolar stimulation of different grid contacts. Motor and sensory responses evoked by single or 60-Hz stimulation and acute therapeutic trial (2 or 3 weeks) of MCS were also carried out through different pairs of contacts, according to the technique described elsewhere [46,47]. During the therapeutic trial, different pairs of grid contacts were tested until the array that induced best analgesic response at lowest threshold was identified. Best analgesic response was always obtained between contacts separated by 1–2 cm, which in two cases were directed perpendicularly and in two other cases in parallel fashion to the MC main axis. In one case (MC3), MCS using multiple combinations of contacts and stimulation parameters, performed during 15 days failed to improve pain. In this case, the grid contacts covering an area of 5 cm in length and 4 cm width should have included the somatotopic representation on the motor cortex of neck, the entire arm and trunk, as described in previous publications [28,46,47]. However, complete deafferentation of the painful territory prevented recognition of its motor and sensory cortical representation that may have included also a modified somatotopy.

Thereafter, patients were returned to the operating room and the craniotomy was re-opened to place a 4-contact plate electrode for chronic stimulation (Resume, Medtronic Inc., Minneapolis, MN, USA), covering precisely the area where best analgesic response had been obtained in the sub-acute therapeutic trial.

Stimulation parameters comprised 90 μs, 40 Hz, 2.0–3.5 V (median, 2.8 V), 1 h ON and 4.0 h OFF stimulation over 24 h [18]. During the therapeutic trial in MC3 stimulation parameters were increased up to 7.0 V and 450 μs, and 130 Hz. In none of the patients MCS induced seizures either during sub-acute or chronic stimulation.

Pain intensity was evaluated by means of the visual analog scale (VAS) in its original graphic form [21,38], the extended version of the McGill pain questionnaire (MPQ), and the Bourhis scale for pain prior to and each month during the first year, and every 6 months thereafter [47]. Changes in scores of pre-operative evaluation

Table 1
Clinical characteristics of studied patients that include pre-operative visual analog scale (VAS) and sensory and sympathetic changes in the painful territory. *Abbreviations:* AL, allodynea; PAN, painful anesthesia; ↓S, hypoesthesia; ↑S, hyperalgesia; ↓T, decreased temperature; Ds, discoloration; Sw, swelling and perspiration; M, Motor assessment scale (0 = paralysis, 5 = normal strength).

Code	Age (years)	Gender	Pre-operative VAS	Etiology and painful territory	History of pain (years)	Local changes	
						Sensory changes	Others
MC 1	34	F	8–10	Brachial plexus trauma C2–T3 left	14	AL, ↑S	↓T, Sw, Ds, M 5/5
MC 2	39	F	10	Hemangiectasy C4–C8 left	6	AL, ↑S	↓T, Sw, Ds, M 5/5
MC 3	52	F	10	Brachial plexus avulsion C5–T1 right	4	PAN	↓T, Sw, Ds, M 0/5
MC 4	42	M	8–10	Brachial plexus avulsion C5–T1 left	1.5	PAN, ↑S	Sw, Ds, M 3/5
MC 5	75	F	10	Scleroderma neuropathy C4–T1 left	15	AL, ↑S, ↓S	↓T, Sw, Ds, M 4/5

VAS, visual analog scale.

Please cite this article in press as: Velasco F et al. Motor cortex electrical stimulation applied to patients with complex regional pain syndrome. PAIN® (2009), doi:10.1016/j.pain.2009.08.024

scales and from the entire follow-up were obtained and expressed as median, maximal, and minimal values. At day 60 or 90, patients entered a double-blind protocol, turning OFF stimulators for 30 days. Patients were selected to enter double-blind maneuver at a given time by lottery number. Statistical changes were evaluated through Wilcoxon rank sum test. Significant changes were considered values below $p < 0.05$ [47].

Trophic sympathetic changes were also evaluated by a qualitative predictive scale.

3. Case presentation

3.1. MC 1

TC was a 34-year-old woman with a 14-year history of type I CRPS in entire right arm secondary to trauma in the arm and shoulder. She referred to her pain as a constant burning sensation, with exacerbations induced by temperature changes. The patient had perspiration in arm and particularly hand, with forearm and hand skin discoloration and swelling. The majority of the time, the patient ranked pain intensity in VAS from 8 to 10.

She had been treated with multiple analgesics, and prior to MC stimulation she was taking morphine sulfate and tramadol in escalating doses. Repeated sympathetic blocks of stellate ganglion induced discrete improvement in pain intensity for only short periods of time.

The patient was operated on in February 1999. The sub-acute stimulation trial reduced pain intensity from 9 to 4. Chronic stimulation was started after the grid was replaced by Resume electrode. Allodynea, perspiration, swelling, and discoloration in right arm completely disappeared after 2 days ON stimulation. When the stimulator was turned OFF during the double-blind period, VAS increased to 8 and sympathetic changes reappeared. During the first year ON stimulation, pain improvement was sustained with VAS score ranking from 1 to 4. The patient re-incorporated into her normal life, but continued taking analgesics.

After a 14-month period, she suddenly returned to her original VAS scores. Cortico-cortical evoked responses could not be elicited by stimulation by means of the pulse generator, and electrode impedance was >2000 ohms. Increase in pulse intensity to 10.5 V induced no objective or subjective sensation. With these data, we presumed the diagnosis of epidural fibrosis around the electrode; thus, the patient was taken back to the operating room and the craniotomy was re-opened. After cleaning a profuse fibrosis around the electrode and repositioning this and the cranial flap, stimulation was re-started. The patient's analgesic response returned to its best level (VAS 1), even when Voltage was decreased from 7.0 to 2.5 V, and sympathetic changes disappeared again. At present, 7 years after onset of MCS, the patient is improved, with a VAS of 1–3, and is back to work and using her arm normally.

3.2. MC 2

RP was a 39-year-old-female with a diagnosis of hemangiectasy (Parkes–Weber syndrome) consisting of arteriovenous shunt-associated to painful peripheral venous dilatation affecting left upper extremity and chest. The patient had CRPS, with the painful area involving the entire left extremity plus pectoral and scapular regions, associated to important forearm and hand cyanotic discoloration, sensation of coldness in hand, and severe perspiration in palm (Fig. 1A). She was treated at the vascular and pain clinics of different hospitals with several treatments including endovascular administration of sclerosant agents, arteriovenous malformation bypass, multiple analgesic medication, and sympathetic blocks,

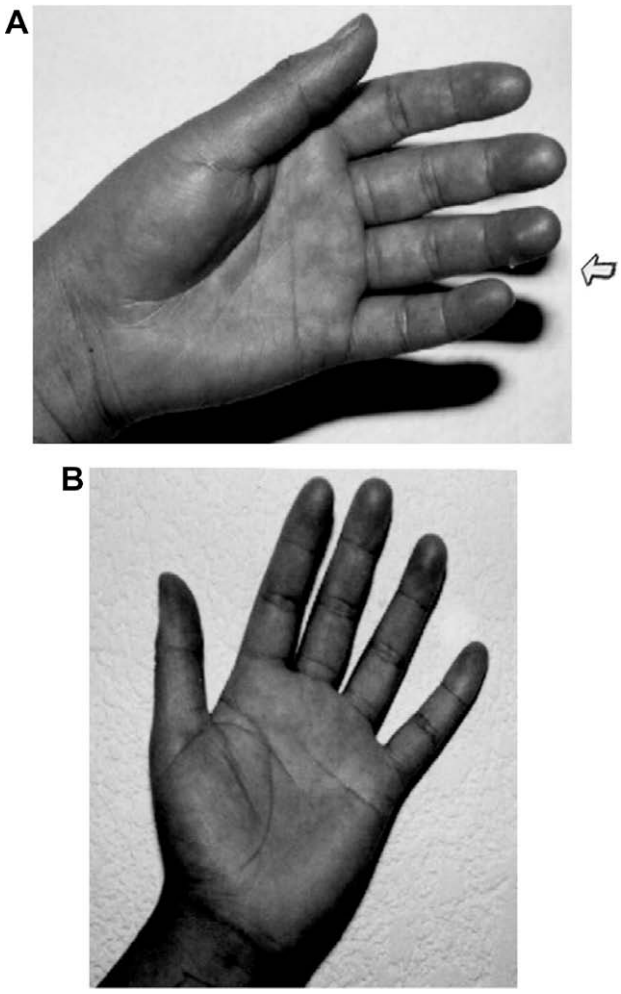

Fig. 1. MC2. Sympathetic changes in hand before and after motor cortex electrical stimulation (MCS). Patient with complex regional pain syndrome (CRPS) presented in the left hand. (A) Swelling, cyanotic discoloration and perspiration (arrow) in hand. (B) Sympathetic changes disappeared after 2 h of MCS.

inducing transient relief of pain that vanished in a few days. The patient referred continuous burning pain with VAS of 10. She had an area of allodynea that extended from forearm to fingertips. The ultimate treatment proposed was amputation of the entire arm.

The patient was seen at our service, entered the protocol, and was implanted with an MC localization grid and the definitive strip during April 1999. Stimulation was so successful that during 5 years, the patient had a VAS of 0. During this time period, arm swelling, perspiration, and cyanotic discoloration disappeared (Fig. 1B). The patient was able to finish her technical career studies and became a stylist, and during this period she was OFF analgesic medication.

In 2004, pain incremented to a VAS of 7, and after testing the battery charge, and neurostimulator impedance and integrity, as well as recording frontal cortico-cortical evoked potentials of similar amplitude to the pre-operative potentials, pulse amplitude was increased to 8 V without significant improvement. Analgesic combinations and nerve and sympathetic blocks induced only mild and transient analgesia.

The patient subsequently visited the Vascular Clinic, where the physician determined that the illness had progressed; thus, the proposal of amputation was once again considered. We re-evaluated the case as a new one, and plain X-ray skull films

Please cite this article in press as: Velasco F et al. Motor cortex electrical stimulation applied to patients with complex regional pain syndrome. PAIN® (2009), doi:10.1016/j.pain.2009.08.024

demonstrated that the superior part of the Resume electrode had migrated backward toward sensory cortex (Fig. 2A and B). In April 2005, the craniotomy was re-opened and the old electrode was replaced with a 20-contact grid. The entire MC localization process was performed by means of the grid, and a meticulous sub-acute stimulation test through different pair of contacts was performed during 2 weeks. There were several pairs of contacts that when stimulated improved the pain; however, one was particularly efficient and rendered the patient a VAS of 2, associated with disappearance of sympathetic changes within minutes. In May 2005, a permanent Resume electrode was again implanted; since that time, the patient has continued to experience complete relief from CRPS, is OFF analgesics, and is back at work.

3.3. MC 3

OG was a 52-year-old female with a past history of right brachial plexus avulsion. Pain was continuous and referred as an excruciating, burning sensation with pressure-elicited allodynea and pin-prick anesthesia of entire limb. Swelling, perspiration, and pale discoloration of forearm and hand were prominent. The patient had no residual motor function in right arm from the shoulder down. She had been treated with carbamazepine, oxcarbazepine, tramadol, oxycodone, and buprenorphine with no pain relief. Sympathetic blocks had also been unsuccessful.

A 20-contact grid was implanted on August 6, 1999. MC localization was jeopardized by the impossibility of performing either sensory evoked potentials (SEP) studies through median nerve or supraclavicular brachial plexus stimulation, or eliciting sensory or motor responses by acute electrical stimulation (ES) through different pairs of contacts. Sub-acute electrical stimulation through multiple combinations of contacts did not improve pain or the associated sympathetic dystrophy.

The patient was rejected from the chronic MCS protocol and instead underwent a C5–T1 dorsal root entry zone transsection (DREZotomy) on the right. During surgery, a complete avulsion of posterior and anterior C5–T1 roots starting at their entrance in lateral spinal grooves was confirmed. Pain relief was significant (VAS diminished from 10 to 3). No modifications in swelling and perspiration were detected after surgery.

3.4. MC 4

JLJ was a 42-year-old male with a diagnosis of left brachial plexus avulsion-associated neuropathic pain. Pain was referred as an aching and burning sensation of the arm with an area of allodynea and excruciating pain involving thumb and index fingers. Pain severity was repeatedly ranked from 8 to 10 in VAS. The patient presented swelling, paleness, muscular atrophy, a sensation of coldness of the entire arm, and cyanosis, swelling, and perspiration in palm (Fig. 3). He had a mild (3/5) paresis of shoulder, elbow, and

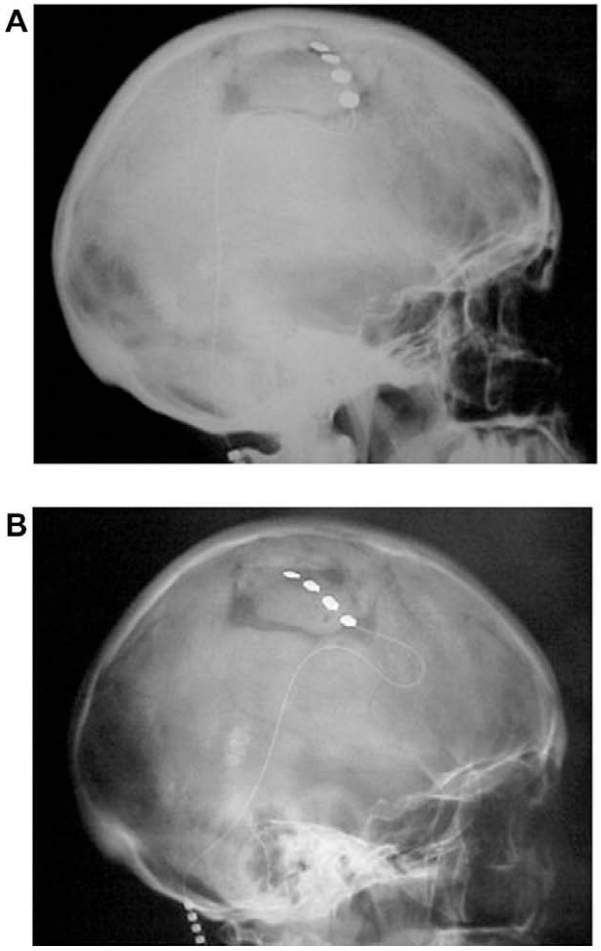

Fig. 2. MC2. (A) Post-operative skull X-ray film after 1st implantation of resume electrode. (B) Five years later, motor cortex electrical stimulation (MCS) lost efficacy and new X-ray film showed posterior displacement of distal part of the electrode that moved away from anterior margin of the craniotomy. This occurred despite that the electrode was fixed to the dura with nylon stitches.

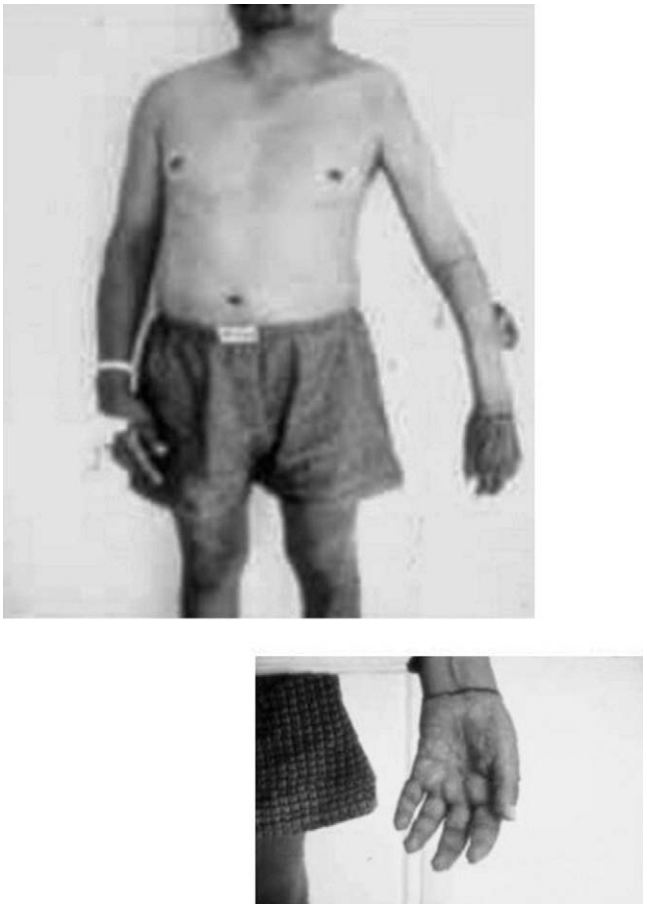

Fig. 3. MC4. Pre-operatively, these were sympathetic changes of entire left arm, with paleness, perspiration, and atrophy of arm and shoulder. Cyanotic discoloration and swelling of hand (close-up). Motor cortex electrical stimulation (MCS) decreased sympathetic changes in arm, but not in hand, which were associated with decrease in pain in arm but not in hand.

Please cite this article in press as: Velasco F et al. Motor cortex electrical stimulation applied to patients with complex regional pain syndrome. PAIN® (2009), doi:10.1016/j.pain.2009.08.024

wrist muscles and paralysis of thumb and index fingers. In addition, the patient experienced anesthesia of C6–C8 dermatomes, allodynea in C5 alternating with areas of hyperesthesia from C4–T2. Multiple analgesic trials to treat pain were not effective. The patient was also administered repeated epidural and sympathetic blockage without improvement.

On October 6, 2000, a 20-contact grid was implanted and thereafter was replaced with Resume electrode; MCS induced pain amelioration. VAS score fell from 10 to 2 and swelling, paleness, and coldness sensation decreased throughout the arm, but the area of allodynea, pain, and cyanotic discoloration persisted in hand. Pain increased to 10 during the OFF period of the double-blind protocol and after a head trauma that caused breaking of the electrode. The electrode was not replaced because the patient wish a definitive lesional operation (inclusive his pain was almost abolish with MCS), so the patient was then proposed for a C5–C7 left DREZotomy to complete pain treatment 2½ years after beginning MCS, which resulted in complete relief of pain and allodynea in hand, but no changes in sympathetic symptoms.

3.5. MC 5

CO was a 75-year-old female with a diagnosis of scleroderma. This illness produced an important CRPS in left arm. Pain increased over time and for the previous 2 years it was intense (VAS of 10), with allodynea in radial forearm and thumb. On physical examination, there was allodynea at C5–C6 dermatomes and hyperalgesia of C4–C5 and C7–T2. There were also scleroderma stigmas with atrophy of hand and forearm muscles and characteristic changes in skin, plus cyanosis, swelling, and perspiration in hand. The patient was treated with carbamazepine, gabapentine, and tramadol without success. Cervical sympathetic blocks were also ineffective.

The patient was operated on October 10, 2003, and a 20-contact grid was placed over the MC. After neurophysiologic studies were completed, a definitive electrode was implanted.

Improvement in pain, allodynea, hyperesthesia, and sympathetic changes was remarkable. VAS fell from 10 to 2. During the double-blind period, pain and CRPS returned to baseline levels. Improvement has been maintained for over 3 years.

4. Results

Table 2 and Fig. 4 summarize the results in our patients. Two patients had CRPS type I syndrome (MC1 and 2), and MC3 and 4 had a type II syndrome, while MC5 had Electromyography (EMG) changes that were most likely scleroderma-related, in which motor function was difficult to assess in view of deformities in joints and skin secondary to the disease's arthritic component. In four cases, the pulse amplitude necessary to obtain pain relief was relatively low (from 2.0 to 3.5 V) with minimal variations during the first year ON stimulation. In the case without analgesic response, increasing the charge density by several folds (130 Hz, 450 μs, and up to 7.0 V) did not result in any analgesic effect.

During a longer follow-up period, two of our patients required a progressive increment in pulse amplitude to maintain the analgesic response. Despite the increments, MCS became ineffective. These two cases were re-evaluated. One of the patients had developed epidural fibrosis that interfered with MCS, which was suspected as by means of the increase in electrodés impedance >2000 ohms and the loss of effect to evoke cortico-cortical potentials by setting the IPG stimulation at 6–10 Hz, 450 μs, and up to 10.5 V [46]. Diagnosis was corroborated at surgery.

In the remaining patient (MC2), plain X-ray film showed migration of the distal part of the electrode outside the area where it was originally placed. Once these problems were identified and solved surgically, MCS regained its efficacy (Fig. 2).

Table 2
Decrements in visual analog scale (VAS) score and sensory changes induced by motor cortex electrical stimulation (MCS) by end of follow-up. Range of improvement, 70–80%; allodynea, and hyperalgesia disappeared or decreased in all patients, while hypoesthesia and anesthesia remained unchanged. Abbreviations equal as for Table 1.

Code	Stimulation parameters	Post-op DVAS rank (%)	Follow-up years	Local changes	
				Sensory modifications	Others modifications
MC 1	40 Hz 2.5 V 90 μs	70 (3)	6	AL disappeared ↑S disappeared	Sw, Ds, ↓T disappeared
MC 2	40 Hz 2.5 V 90 μs	80 (3)	6	AL disappeared ↑S disappeared	Sw, Ds, ↓T disappeared
MC 3	40–130 Hz 3–7 V 90–450 μs	0 (10)	Not implanted	No changes	No changes
MC 4	40 Hz 2–3.5 V 90 μs	70 (2)	3	↑S disappeared PAN unchanged	Sw, Ds. disappeared
MC 5	40 Hz 2–3.5 V 90 μs	80 (2)	3	AL, ↑S disappeared ↓S unchanged	Sw, Ds, ↓T disappeared

DVAS = delta visual analog scale.

MC4 experienced a stable analgesic response in the entire arm, but allodynea in thumb area persisted unchanged during the 3 years ON-MCS. The patient was finally treated with left C5–C7 DREZotomy that improved the pain but not discoloration and swelling in hand.

In other words, in all patients in whom MCS was effective to induce analgesia, it also produced a decrease of hyperalgesia, allodynea, and sympathetic changes in the painful territories. These cases had preserved motor function and no areas of anesthesia. In contrast, cases in which areas of anesthesia and paralysis were included in the painful territory, MCS had no effect on pain, or on sensory or sympathetic changes of denervated areas.

Fig. 4 shows the results of evaluations performed prior to surgery (baseline), a month after onset of MCS, during the OFF-stimulation period of the double-blind trial, and at the end of the follow-up period (36–72 months) by VAS, MPQ, and Bourhis scales. Results are presented in percentage of maximal possible score for each scale. It can be observed that the values of all scales decreased during ON-MCS periods, except the MPQ in MC2 at 1 month, while these values tended to return to baseline levels during the OFF-stimulation period of the double-blind period, except for MPQ in MC3. At the end of the follow-up period, improvement in VAS oscillated between 44% and 80%, MPQ score ranged from 35% to 89%, and the Bourhis score, from 17% to 52%. It was remarkable that there was no correlation in decrements of VAS and decrements in scores of other scales in individual cases.

No immediate complications were seen in these patients, while at the long-term one patient experienced a traumatic fracture of the electrode at 3 years, one had epidural fibrosis at 14 months ON stimulation, and another had an electrode migration 5 years after electrode implantation.

5. Discussion

5.1. Efficacy of MCS in treating CRPS

Although the reduced number of cases included in the present report comprises an obvious limitation, our experience may be of interest, considering that there has been only one case reported of type II CRPS treated successfully with MCS in the literature published in English [40]. MCS was effective in controlling pain,

Please cite this article in press as: Velasco F et al. Motor cortex electrical stimulation applied to patients with complex regional pain syndrome. PAIN® (2009), doi:10.1016/j.pain.2009.08.024

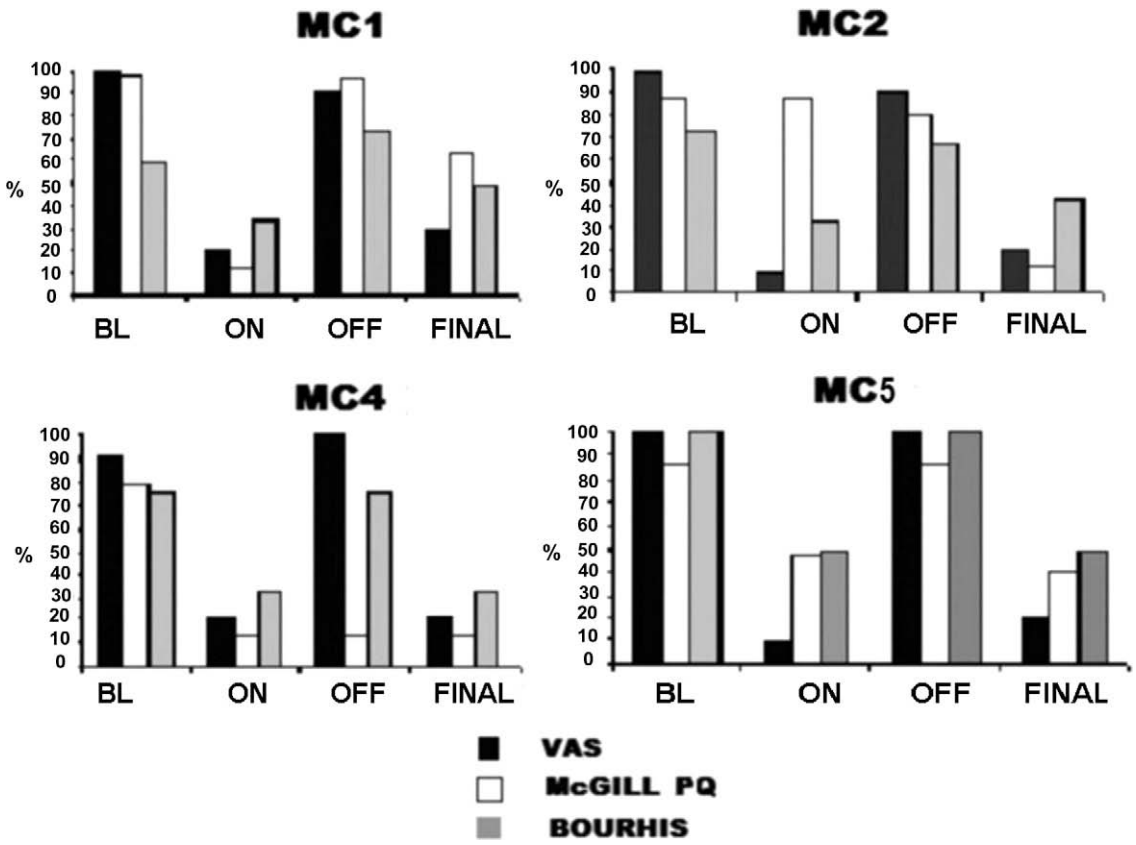

Fig. 4. Follow-up of four patients with chronic motor cortex electrical stimulation (MCS), by means of visual analog scale (VAS) (dark columns), McGill pain questionnaire (MPQ) (clear columns), and Bourhis scale (dashed columns). BL, baseline levels at 1-month ON stimulation; DB, during the period OFF stimulation of the double-blind maneuver and final evaluation performed at 36–72 months. Results are presented as percentage of maximal possible score for each scale.

reducing or abolishing allodynea, and reducing sympathetic changes in CRPS of various etiologies, such as traumatic injuries of brachial plexus, hemangiectasy, and scleroderma-associated neuropathy. Decrease in MCS-induced allodynea and hyperalgesia has been related with favorable outcome [47], as has been normalization of threshold for temperature changes in the painful territory [13].

Decrease in CRPS-related sympathetic disturbances induced by MCS appears to have the same prognostic value as changes in sensory abnormalities. The remarkable and unexpected improvement in CRPS-associated sympathetic symptoms could not be quantitatively measured. Indeed, there are no clinimetric scales for evaluating sympathetic changes alone or in combination with pain. In the cases reported in this study, attempts to quantify these changes through oximetry, microcirculation Doppler studies, and galvanic skin response for perspiration and bone densitometry did not provide consistent data. However, changes in color, swelling, and perspiration were obvious for the patient and examiners and occurred to be time-locked with MCS initiation and termination. They were evident only in painful territories that preserved partially or totally their motor innervations, and not in those with complete-dennervation. In fact, in our two cases in which MCS did not improve sympathetic symptoms, these were confined to a totally paralyzed territory. In MC3, motor and sensory dennervation included the entire painful territory (anesthesia dolorosa) and in MC4, the territory with complete-dennervation (C5–C7) sympathetic disturbances remained unchanged. In both cases, dorsal and ventral roots corresponding to areas with complete-dennervation were found avulsed during a DREZotomy surgical procedure, performed after MCS had failed.

In contrast, in the territories with partial denervation including the entire arm, shoulder, and upper chest as in MC1, 2, and 5, or restricted to proximal arm and shoulder as in MC4, both pain and sympathetic changes were significantly improved only in the territory with partial denervation (Fig. 3).

5.2. Mechanism of action

A central analgesic mechanism has been proposed on the basis of comparative Positron Emission Tomography (PET) studies performed before and after MCS. Neuronal activation (hyper-metabolism) of cortical and thalamic areas related with sensory input (sensory thalamus) and emotional interpretation of pain (cingulated cortex) was induced by MCS [15,16,32,33].

Moreover, it has been reported that activation of thalamus and cingulated cortex occurs differentially in cases with good analgesic response and not in those that have failed [33]. Although this hypothesis has been well elaborated, it could not explain the observation that totally denervation of painful territories prevents analgesia induced by MCS in our cases.

Other hypotheses to explain MCS's analgesic effect, is the control of sensory input at the level of the spinal cord through descending fibers originated in motor cortex (MC) [23,30]. Cortical control on spinal cord sensory input has been extensively demonstrated through anatomical, physiological end neuro-chemical studies in experimental animals [2,12,14,18,19,26,31,39]. Cortical projections terminate in all spinal cord laminae and synapse with spinal cord inhibitory interneurons [3,14,27]. In part, the cortical control on spinal neurons uses brain stem connections [1,9].

Most studies have focused on the inhibitory effect of MC on dorsal horn neuronal activity and there is experimental evidence that MCS inhibits dorsal neurons response to nociceptive stimuli [39]. In man, MCS has been shown to increase the metabolism of areas placed in the ventral mesencephalon [32], which may indicate that

Please cite this article in press as: Velasco F et al. Motor cortex electrical stimulation applied to patients with complex regional pain syndrome. PAIN® (2009), doi:10.1016/j.pain.2009.08.024

part of the analgesic response is mediated by descending fibers beyond the thalamic sensory nuclei. Conceivably, in those cases with CRPS with minimal or partial peripheral nerve lesion, descending cortical fibers would be acting on a preserved mechanism at the dorsal root entry zone (DREZ), while in the case of complete avulsion of the dorsal root this mechanism would be disrupted and therefore MCS results ineffective. In cases MC3 and 4, MCS was indeed inefficient in controlling pain in painful territories with complete nerve avulsion. It is true that successful analgesic effect of MCS in plexus avulsion have been described in other reports [28,29]. However, there is no description of the degree of deafferentation in the reported cases, particularly motor deficits, because some had amputated limbs. Besides, 3 out of 6 patients had poor outcome (10% VAS improvement) and the other cases had a variable degree improvement. These cases were not reported to have CRPS sympathetic changes. Our patients with preserved motor function had excellent results, the one with partial motor deafferentation of the painful area had mild improvement and only the patient with complete deafferentation had no response.

The hypothesis of a disrupted DREZ gate mechanism explaining the failure of MCS on pain control is debatable, since DREZotomy has been found highly effective in cases of pain secondary to plexus nerve avulsion [41]. In our own cases, DREZ operation relieved pain in the territories with total denervation, accompanied by complete avulsion of dorsal and ventral roots found during surgery.

A possible alternative explanation may be that ventral roots play some role in pain control. It might be in part mediated by sympathetic mechanisms initiated in the lateral horn, with sympathetic fibers exiting in ventral roots and profusely communicated to other segmental spinal cord levels. This goes along with the observation that sympathetic changes often extend beyond the dermatomes of the damaged roots, and that spinal cord stimulation (SCS) improves CRPS beyond the stimulated spinal cord segments [4,5]. Another possibility is that unmyelinated fibers traveling in the ventral roots may convey sensory information as has been proposed by others [10,11,22] although this is controversial.

5.3. Analgesic effect in MCS

MCS loss efficacy over time has been attributed to plastic changes in the painful area's cortical representation [20]. To deal with this phenomenon, several leads have been used in a complicated and aggressive stimulation program. In our cases, the MCS analgesic effect remained fairly stable for periods up to 6 years, and decreased efficacy in some cases was derived from complications that could be identified and treated (traumatic breaking of the electrode, epidural fibrosis, and electrode displacement). We would recommend exploring these possibilities prior to engaging in more complicated processes.

5.4. Undesirable events

As mentioned above, 3 of our patients presented undesirable events:

1. Electrode breakage has been a complication reported in all procedures that use electrical stimulation through implanted electrodes. Several recommendations have been made to minimize this possibility, such as fixing the connector cable and electrode junctions to the bone at the level of the mastoid, placing the electrode subcutaneously in a deeper layer, avoiding loops to reduce the possibility of skin erosions, etc. However, electrode breakage secondary to a direct trauma over its subcutaneous trajectory during an assault seems unavoidable risk.
2. In regard to the epidural fibrosis presented in one case and the electrode migration presented in another case, these may be in part caused by the available hardware used for MCS. We are using a tetrapolar plate electrode designed for SCS, which is rigid, thick and has no space to place sutures to be fixed to the Dura. The design of a 12-contact-electrode for cortical recording and stimulation, that would avoid a two surgical stage procedure, it could be more flexible to adapt to cortical convexity and have a rim to place sutures that will fix it to the Dura, is already under consideration in several companies that built neurostimulators.

6. Conclusions

MCS is efficient in controlling CRPS regardless of its etiology. Vast painful territories may be covered using a single tetrapolar electrode. Sensory and sympathetic changes accompanying CRPS are decreased by MCS, and this effect may serve as a predictive factor. The mechanism of action probably involves spinal cord structures including spinal sympathetic nucleus and ventral roots.

Acknowledgments

The authors are grateful to Pr. Patrick Mertens, M.D., Ph.D., Neurosurgeon of Hôpital Neurologique-Lyon University, France, for review and commentary on the manuscript, and to Maggie Brunner, M.A., who kindly corrected its grammar and style.

The work was partially supported by the Research Division of the General Hospital of Mexico. This research has no conflict of interest.

References

[1] Akintunde A, Buxton DF. Origins and collateralization of corticospinal, corticopontine, corticorubral and corticostriatal tracts: a multiple retrograde fluorescent tracing study. Brain Res 1992;586:208–18.
[2] Andersen P, Eccles JC, Sears TA. Cortically evoked depolarization of primary afferent fibers in the spinal cord. J Neurophysiol 1964;27:63–77.
[3] Antal M, Sholomenko GN, Moschovakis AK, Storm-Mathisen J, Heizman CW, Hunziker W. The termination pattern and post-synaptic targets of rubrospinal fibers in the rat spinal cord: a light and electron microscopic study. J Comp Neurol 1992;325:22–37.
[4] Barolat G, Schwartzmann R, Woo R. Epidural spinal cord stimulation in the management of reflex sympathetic dystrophy. Appl Neurophysiol 1987;50:442–3.
[5] Barolat G, Schwartzmann R, Woo R. Epidural spinal cord stimulation in the management of reflex sympathetic dystrophy. Stereotact Funct Neurosurg 1989;53:29–39.
[6] Baron R, Wasner G. Complex regional pain syndromes. Curr Pain Head Rep 2001;5:114–23.
[7] Baron R, Fields HL, Janig W, Kitt C, Levine JD. National institutes of health workshop: reflex sympathetic dystrophy/complex regional pain syndromes – state of the science. Anesth Analg 2002;95:1812–6.
[8] Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. J Neurosurg 2004;100:254–67.
[9] Catsman-Berrevoets CE, Kuypers HG. A search for corticospinal collaterals to thalamus and mesencephalon by means of multiple retrograde fluorescent tracers in cat and rat. Brain Res 1981;218:15–33.
[10] Coggeshall RE, Appleubaum ML, Fazen M, Stubbs 3rd TB, Sykes MT. Unmyelinated axons in human ventral roots, a possible explanation for the failure of dorsal rhizotomy to relieve pain. Brain 1975;98:157–66.
[11] Coggeshall RE. Afferent fiber in the ventral root. Neurosurgery 1979;4:443–8.
[12] Coulter JD, Jones EG. Differential distribution of corticospinal projections from individual cytoarchitectonic fields in monkey. Brain Res 1977;129:335–40.
[13] Drouot X, Nguyen JP, Peschanski M, Lefaucheur JP. The antalgic efficacy of chronic motor cortex stimulation is related to sensory changes in the painful zone. Brain 2002;125:1660–4.
[14] Fetz EE. Pyramidal tract effects on interneurons in the cat lumbar dorsal horn. J Neurophysiol 1968;31:69–80.
[15] García-Larrea L, Peyron R, Mertens P. Positron emission tomography during motor cortex stimulation for pain control. Stereotac Funct Neurosurg 1997;68:141–8.
[16] García-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 1997;83:259–73.

[17] Harney D, Magner JJ, O'Keeffe D. Complex regional pain syndrome: the case for spinal cord stimulation (a brief review). Injury 2005;36:357–62.
[18] Hayes NL, Rustioni A. Descending projections from brain stem and sensorimotor córtex to spinal enlargements in the cat. Single and double retrograde tracer studies. Exp Brain Res 1981;41:89–107.
[19] Jones SL, Gebhart GF. Inhibition of nociceptive transmission from the midbrain, pons and medulla in the rat: activation of descending inhibition by morphine, glutamate and electrical stimulation. Brain Res 1988;460:281–96.
[20] Henderson JM, Boongird A, Rosenow JM, LaPresto E, Rezai AR. Recovery of pain control by intensive reprogramming after loss benefit from motor cortex stimulation for neuropathic pain. Stereotact Funct Neurosurg 2004;82:207–13.
[21] Huskisson EC. Measurement of pain. Lancet 1974;2:1127–31.
[22] Ito H, Hasewaga T, Ikeda K, Kashiwara K, Yamamoto S, Coggeshall RE. A possible explanation for the failure of dorsal rhizotomy to relieve pain (abstract). Appl Neurophysiol 1979;42:315.
[23] Jouttonen K, Gockel M, Silen T, Hurri H, Hari R, Forss N. Altered central sensorimotor processing in patients with complex regional pain syndrome. Pain 2002;98:315–23.
[24] Kemler MA, Reulen JP, Barendse GA, Van Kleef M, De Vet HC, Van den Wildenberg FA. Impact of spinal cord stimulation on sensory characteristics in complex regional pain syndrome type I: a randomized trial. Anesthesiology 2001;95:72–80.
[25] Kumar K, Nath RK, Toth C. Spinal cord stimulation is effective in the management of reflex sympathetic dystrophy. Neurosurgery 1997;40:503–8.
[26] Lindblom VF, Ottosson JO. Influence of pyramidal stimulation upon the relay coarse cutaneous afferents in the dorsal horn. Acta Physiol Scand 1956;38:309–18.
[27] Lundberg A, Norssell V, Voorhoeve P. Pyramidal effects on lumbosacral interneurons activated by somatic afferents. Acta Physiol Scand 1962;56:220–9.
[28] Nguyen JP, Lefaucheur JP, Decq P, Keravel Y. Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Cortical relations between clinical, electrophysiological and anatomical data. Pain 1999;82:245–51.
[29] Nuti C, Peyron R, García-Larrea L, Brunon J, Laurent B, Sindou M, Mertens P. Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy. Pain 2005;118:43–52.
[30] Ohmoto T, Nakao Y, Sakurai M. Electrical stimulation of the posterior limb of the internal capsule for treatment of thalamic pain. Brain Nerve 1985;35:1009–16.
[31] Peng YB, Lin Q, Willis WD. Effects of GABA and glycine receptor antagonists on the activity and PAG-induced inhibition of rat dorsal horn neurons. Brain Res 1996;736:189–201.
[32] Peyron R, García-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, Mauguiere F, Laurent B. Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. Pain 1995;62:275–86.
[33] Peyron R, Faillenot I, Mertens P, Laurent B, García-Larrea L. Motor cortex stimulation in neuropathic pain. Correlations between analgesics effect and hemodynamic changes in the brain. A PET study. Neuroimage 2007;34:310–21.
[34] Robaina FJ, Rodríguez JL, de Vera JA, Martín MA. Transcutaneous electrical nerve stimulation and spinal cord stimulation for pain relief in reflex sympathetic dystrophy. Stereotact Funct Neurosurg 1989;52:53–62.
[35] Rho RH, Brewer RP, Lamer TJ, Wilson PR. Complex regional pain syndrome. Mayo Clin Proc 2002;77:733–4.
[36] Sánchez-Ledesma MJ, García-March G, Díaz-Cascajo P, Gómez-Moreta J, Broseta J. Spinal cord stimulation in deafferentation pain. Stereotact Funct Neurosurg 1989;53:40–5.
[37] Schady W, Sheard A, Hassell A, Holt L, Jayson MI, Klimiuk P. Peripheral nerve dysfunction in scleroderma. Q J Med 1991;80:661–75.
[38] Scott J, Huskisson EC. Graphic representation of pain. Pain 1976;2:175–84.
[39] Senapati AK, Huntington PJ, Peng YB. Spinal dorsal horn neuron response to mechanical stimuli is decreased by electrical stimulation of the primary motor cortex. Brain Res 2005;1036:173–9.
[40] Son UC, Kim MC, Moon DE. Motor cortex stimulation in a patient with intractable complex regional II with hemibody involvement. Case report. J Neurosurg 2003;98:175–9.
[41] Sindou M, Blondet E, Emery E, Mertens P. Microsurgical lesioning in the dorsal root entry zone for pain due to brachial avulsion: a prospective series of 55 patients. J Neurosurg 2005;102:1018–28.
[42] Stanton-Hicks M, Baron R, Boas R, Gordth T, Harden N, Hendler N, Koltzenburg M, Raj P, Wilder R. Complex regional pain syndromes: guidelines for therapy. Clin J Pain 1998;14:155–66.
[43] Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir (Wein) 1991;52:369–75.
[44] Tsubokawa T, Katayama Y, Yamamoto T. Treatment of thalamic pain by chronic motor cortex stimulation. Pacing Clin Electrophysiol 1991;14:131–4.
[45] Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 1993;75:396–401.
[46] Velasco M, Velasco F, Brito F, Velasco AL, Nguyen JP, Márquez I, Boleaga B, Keravel Y. Motor cortex stimulation in the treatment of deafferentation pain. Localization of the motor cortex. Stereotact Funct Neurosurg 2002;79:146–67.
[47] Velasco F, Argüelles C, Carrillo-Ruiz J, Castro G, Velasco AL, Jiménez F, Velasco M. Efficacy of motor cortex stimulation in the treatment of neuropathic pain: a double blind randomized trial. J Neurosurg 2008;108:698–706.
[48] Weber FP. Haemangiectactasis hypertrophy of limbs. Congenital phlebarteriectasis and so-called congenital varicose veins. Br J Child Dis 1918;15:13–7.

Please cite this article in press as: Velasco F et al. Motor cortex electrical stimulation applied to patients with complex regional pain syndrome. PAIN® (2009), doi:10.1016/j.pain.2009.08.024