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Neuromodulation in Treating Complex Regional Pain Syndrome: A Critical Review of the Evidence

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Abstract

Background and objectives: The management of complex regional pain syndrome (CRPS) remains a challenging task therefore a large number of interventions have been investigated. Lately, invasive and non-invasive neuromodulation have been coming up as an alternative for some patients even as an add-on treatment to medicines or physical therapy. The objective of this review is to evaluate the evidence of its effectiveness in CRPS chronic pain management.

Methods: We have used key words referring to neuromodulation techniques and CRPS to select studies from Medline, Lilacs and Cochrane Library databases. All relevant articles which have described any kind of neuromodulation as CRPS primary treatment have been reviewed by two independent researchers to assign the level of evidence according to Oxford Level of Evidence. A third researcher was consulted in dubious cases to get to the final conclusion.

Results: Although a variety of methods and devices have been used, the evidences are still poor. There is no level 1 study which confers grade A of recommendation for any method of neuromodulation in the CRPS treatment. Repetitive transcranial magnetic stimulation (rTMS) over the motor cortex and spinal cord stimulation (SCS) were the techniques with the best grade of recommendation (B or C).

Conclusion: The literature still lacks high-quality evidence supporting neuromodulation effectiveness in CRPS pain treatment. We found only a few studies that had approached this issue properly. Those facts themselves were the main limitation of this study and of those that must be coming soon. High-quality multicentre trials ought to be performed for definitive conclusions.

Keywords: Complex regional pain syndrome; Neuromodulation therapy; Evidence and recommendation grades

Introduction

Complex Regional Pain Syndrome (CRPS) is an array of neuropathic pain conditions that has been known by many names such as Sudeck's Atrophy, Reflex Sympathetic Dystrophy Syndrome and Causalgia. This potential debilitating disease can be very painful and often arises after trauma, surgery or a limb immobilization. It is believed that about 10–20% of cases it becomes chronic and resistant to any treatment [1]. According to this, the hallmarks of CRPS are continuous pain and mechanic hiperalgesia which are disproportional to the inciting event. Besides that, they are coupled to a myriad of symptoms and signs of sensory, motor and autonomic disturbances, with or without trophic changes [2]. The current IASP-criteria (Budapest criteria), which is based only on clinical dates, can detect CRPS with 85% sensitivity and 70% specificity (**Table 1**) [1,3-7].

Although the pathogenesis of CRPS is still unknown, it probably includes changes in all central nervous system, particularly in the brain. Predisposing factors are still uncertain but they may involve tendency toward increased sympathetic activity and genetic predisposition like HLA type (HLA-B62 and HLA-DQ8) [8]. Three conditions are deemed important: a lasting painful injury, a propensity to developing CRPS and an unusual autonomic response to pain. Under normal conditions an injured tissue reflexively leads sympathetic answer of peripheral vasoconstriction to decrease blood loss and swelling. Subsequently it gives way in favor of vasodilatation and increased capillary permeability, which will support the tissue recovery. By unknown reasons, the initial injuries in CRPS patients trigger off continuing and improper sympathetic nervous system answers; probably it is associated to central disrupting of nociceptive impulses from wide dynamic range neurons located in spinal cord. It has also been suggested that changes in N-methyl-D-aspartate (NMDA) receptor are involved in central nervous system (CNS) sensitization process enhanced by high levels of glutamate which promotes wind-up and further CNS sensitization [9,10]. Inappropriate and sustained vasoconstriction consequently will result in an improper circle of ischemia – pain – sympathetic discharge – vasoconstriction. Usually, the local reaction to trauma exacerbates this process by releasing large and substantial amounts of pro-inflammatory mediators such as: histamine,

serotonin and bradykinin. The final outcome is a swollen, sore, stiff, atrophic and nonfunctioning limb. These central changes may be subsumed under the heading of neuroplasticity and sensitization.

Table 1 IASP Clinical diagnostic criteria for CRPS (Budapest Criteria).

General definition: CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that that is seemingly disproportionate in time or degree to the usual course of any know trauma or other lesion. The pain is regional (not in specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over the time.	
To make the clinical diagnosis, the following criteria must be met:	
1	Continuing pain, which is disproportionate to any inciting event
2	Must report at least one symptom in three of the four following categories:
	a) Sensory: Reports of hyperesthesia and/or allodynia
	b) Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
	c) Sudomotor/edema: Reports of edema and/or sweating changes and/or sweating asymmetry
	d) Motor/trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3	Must display at least one sign at time of evaluation in two or more of the following categories:
	a) Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
	b) Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
	c) Sudomotor/edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
	d) Motor/trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
There is no other diagnosis that better explains the signs and symptoms.	

There will be direct consequences of chronic pain input resulting in reorganization of sensory, motor or autonomic brain regions [2,11]. In addition patients show operant conditioning during the course of CRPS. The individual experience, that the movement of the affected joints is invariably painful, it will reinforce a fear to move. This learned behavior surely contributes to the motor symptoms in CRPS. In recent years, numerous studies have reported anatomical and functional brain changes in CRPS patients using either transcranial magnetic stimulation (TMS), magnetic resonance imaging (MRI) or functional MRI (fMRI) [2,12-16]. Some of these studies have reported that MRI was able to show changes in gray matter structure and volumes of many pain-related structures counting: a) orbital frontal gyrus, b) dorsomedial prefrontal cortex, c) dorsal insula, d) motor gyrus, e) cingulated gyrus, f) dorsal putamen and, g) hypothalamus [12,13]. Furthermore, it was reported that a complex cortical network is activated through pin-prick hyperalgesia in CRPS patients, which is believed to be made by areas involved in behavior, endocrinology, cognitive, nociceptive, and motor processing. Obviously these finds could explain many motor, endocrine, emotional and behavioral changes often in CRPS patients [2]. In addition to significant advances in understanding the pathophysiology, it opens a perspective for new targets and therapeutic strategies.

Although a variety of interventions has been described, there isn't any reasonable consensus concerning the most favorable kind of management, medicines and procedures to treat CRPS. Due to the current absence of high-quality evidences of most therapies effectiveness, there is no reasonable standard of care treatment protocol and larger trials are lacking [14]. Despite of that, they are considered as suitable the most therapies and techniques that involve functional restoration such as pain management, physical, psychological and behavioral rehabilitation. It must be interdisciplinary, individualized and focused in many aspects of the personal life of the patient. The goals' approaches are pain relief and full functional, emotional, psychosocial and professional rehabilitation. A case-by-case analysis considering benefits and risks must be performed before treatment planning [6]. It is known that the constant, gradual and steady activation of pre-sensorimotor cortices, by enhanced motor imaginary and visual tactile discrimination, can promote the functional restoring. According to this, very gentle active movements progressing from active range of motion are strongly recommended. The progressive desensitization induces greater range of motion, pain relief, better discrimination and function improvement. The idea is to reset the "altered central processing" and "neglect" areas in the nervous system restoring sensibility and motor function [6].

In order to manage CRPS chronic pain, various medications and a wide range of non-invasive and invasive interventions are available [6,17-20]. However, high quality evidence is lacking for any routine recommendation [21,22].

Many drugs, from different pharmacological classes, have been proposed to treat CRPS pain such as corticosteroids, anti-inflammatory drugs, anticonvulsants (gabapentin, pregabalin and carbamazepine), tricyclic antidepressants (desipramine, imipramine, amitriptyline and nortriptyline), selective serotonin reuptake inhibitors antidepressants (sertraline, fluoxetine, citalopram and escitalopram), serotonin and norepinephrine reuptake inhibitors antidepressants (duloxetine and venlafaxine), opioids painkillers (morphine, tramadol, oxycodone, methadone, fentanyl), bisphosphonates drugs, N-methyl-D-aspartate antagonists (ketamina, memantine and dextromethorphan), adrenergic drugs (clonidina), PDE5 inhibitor (tadafil), calcitonin, calcium channel blockers, beta-blockers, sympatholitic agents, sodium channel blocking agents (lidocaine), GABA agonists (baclofen). Although many drugs are very helpful (especially if associated to a rehabilitation program), none of them have promoted significant alterations in syndrome course [3,6,10,21-23].

The classical techniques of sympathetic activity blocking are still a subject of controversy and their real effectiveness has never been proved. There is low quality of evidence favoring

ganglion blocks (using local anesthetic) or intravenous regional sympatholysis (using guanethidine, bretylium or reserpine) to improve pain or function. Furthermore, controlled trials have never succeeded in proving the effectiveness of either guanethidine intravenous infusion or surgical sympathectomy, which sometimes are associated to high rates of adverse events [21].

In recent years, neuromodulation has been increasingly used as a new strategy to treat CRPS chronic pain though the evidences are still weak. These procedures for pain relief are either non-invasive or invasive and most of the times are considered as last resort therapy for patients whose long-term treatment was ineffective. It involves modulation of all aspects of the painful experience by stimulating or inhibiting specific targets in the central nervous system as pain pathways relays or modulatory nucleus. The invasive procedures refer to implantable devices (electrodes connected to a neurostimulator) such as peripheral nerve stimulation (PNS), dorsal root ganglia stimulation (DRGS), spinal cord stimulation (SCS), motor cortex stimulation (MCS) and deep brain stimulation (DBS). Currently, the most popular non-invasive techniques are: transcutaneous electrical nerve stimulation (TENS), cranial electrotherapy stimulation (CES), reduced impedance non-invasive cortical electrostimulation (RINCE), transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS) and deep transcranial magnetic stimulation (dTMS).

Although invasive neuromodulation has been considered more efficient and powerful, it requires longer training, specialized staff and it is more costly. It also has high complication rates which are related to surgical procedures such as infections, equipment failures, local pain in the implantation site and the need of replacement of its components [24-26].

Currently, there is no consensus regarding the grade of recommendation for neuromodulation techniques in CRPS treatment. Many interventions have been assessed; however there is a wide range and contradictory conclusions from the major trials, systematic reviews and meta-analysis studies. To draw a reliable conclusion, a critical analysis of these studies is necessary.

Objective

The objective of this paper is to make a critical narrative review evaluating the quality of evidences regarding neuromodulation effectiveness in CRPS chronic pain treatment.

Methods

Article selection

In order to find the best evidence level of each neuromodulation method, we have used key-words referring to neuromodulation effectiveness in CRPS treatment to select studies published in Medline, Lilacs and Cochrane Library databases. All articles considered relevant were reviewed by two independently researchers to assign the level of evidence if they had English abstract and have described neuromodulation as a primary treatment. It has included randomized controlled trials, meta-analyses studies, systematic or narrative reviews, prospective and retrospective case series and case-reports. A third researcher was consulted in doubtful cases to draw a final conclusion.

Levels of evidence and recommendation grades

The levels of evidence and recommendation grades which were have used here were in agreement with Phillips [Oxford Centre for Evidence-based Medicine – Levels of Evidence] [27] **(Table 2)**.

Table 2 Oxford level of evidence.

Level	Description	Recommendation Grade
1a	Systematic review with homogeneity of RCTs	**A: Level 1.**
1b	Individual RCT with narrow CI	(excellent level of evidence to recommend the routine use)
1c	All or none	
2a	Systematic review with homogeneity of cohort studies	**B: Level 2 or 3.**
2b	Individual cohort study: low quality RCT (eg, <80% follow-up)	**Extrapolations from level 1 study.**
2c	Outcome research: ecological studies	(Reasonable evidence supporting the recommendation. Clear benefits in action choice in relation to the risk of damage)
3a	Systematic review with homogeneity of case-control studies	--
3b	Individual case-control studies	
4	Case series: poor quality cohort or case-control studies	**C: Level 4.**
		Minimum satisfactory evidence for or against the action. The risks do not justify the widespread recommendation
5	Expert opinion omitting explicit critical appraisal (includes opinion based upon physiology, bench research, or first principles). Inclusive studies	**D: Level 5.**
		Evidence to dismiss the recommendation

RCT: Randomized Controlled Trail, CI: Confidence Interval.

Results

Using different combinations between key words which refer to neuromodulation and SCDR pain treatment (such as neurodulation, TENS, CES, RINCE, tDCS, rTMS, dTMS, PNS, SCS, DRGS, MCS and DBS) we have got hundred twenty-four eligible articles including six randomized controlled trial, two meta-analyses studies and twelve systematic reviews. After

excluding articles that were not related to the topic and those where the disease, treatment or results were improperly described; thirty-nine articles were finally reviewed and graded **(Appendix 1)**.

All randomized controlled trial, meta-analyses and systematic reviews studies found were included. Repetitive casuistic in different articles were reviewed and graded the main study. Thirteen prospective case series and seven case-reports (considered relevant because of the absence of better evidences) were also included.

No study approaching neuromodulation as CRPS pain primary treatment was graded as level A of evidence. The best level of evidence and recommendation was set up to SCS and rTMS technics which we have graded as B. Every other approach has got either grade C or D level of recommendation.

Discussion

Currently, the recommendation grades of many neuromodulation modalities to treat CRPS based on evidences are controversial. The best evidences and the highest degree of recommendation refers to SCS in treating refractory patients, although assigned degrees range from grade A28 to grade C21. In fact, carrying out a critical assessment of literature, there is no level 1 study which confers grade A of recommendation for any method of neuromodulation in the CRPS treatment.

Repetitive Transcranial Magnetic Stimulation (rTMS)

The evidences of positive effects on CRPS pain Pleger [28-30] and Picarelli [31,32] favoring rTMS at high frequency over the motor cortex were classified as strong by Cossins [29], though O'Connell [21,22] has rated them as very low quality of evidence (downgraded for the small sample size, short duration of follow up, small and short-term analgesic effect). Furthermore, the clinical effects do not appear to be significant to change either syndrome development or quality of life. Even multiple-session of rTMS did not consistently reveal to be effective [21,31,32]. In agreement to this, it has been reported that CRPS pain improvement only occurs during rTMS sessions [31,32]. It is possible that repeated sessions held periodically could be more effective, but at this time there is no high quality trial addressing this question. Despite rTMS be considered a simple, inexpensive and safe therapy; dissemination of stimulus or seizures from the target have been reported [31,32]. Based on the best evidences, rTMN would be better graded as level B or C of recommendation.

TENS, CES, RINCE and tDCS

According to O'Connell (2014) the available evidence suggests that TENS, CES, RINCE, tDCS, rTMS at low frequencies or over the pre-frontal cortex, are not effective in CRPS patients [22]. In fact, most trials assessing its effects on chronic or CRPS pain have few heterogeneous patients treated, and the conclusions are negative, inconsistent or inconclusive. Besides that, the follow-up times were usually short, the parameters of stimulation and targets were heterogeneous, many of them were not randomized, and the different evaluation methods make difficult to compare results or properly put them together in a meta-analyses study. Therefore, these methods have level C or D of recommendation.

Peripheral Nerve Stimulation (PNS)

The evidences to graduate PNS as grade C of recommendation in CRPS comes from a single prospective non-controlled series [33,34] and some case reports which have informed pain good relief when it was restricted to a major nerve division [35,36]. Although function and atrophic changes are not affected, activity level and vasomotor improvement were reported.

Stimulation of Dorsal Root Ganglia (DRGS)

Although DRGS has been proposed as an efficient strategy to get pain relief in CRPS patients, the current evidences are still weak and based on few case reports and small uncontrolled studies to treat chronic pain or CRPS patients [37-42]. Van Buyten [42] has reported the results of DRGS of eight patients with successful trial stimulation from eleven CRPS patients that were enrolled in a large multicenter study to treat chronic pain from different etiologies. After a year, at least 50% pain relief was reported in 75% of the subjects. In addition, it had positives effects on mood, quality of life, mobility and several sympathetically signs. Apparently, DRGS could have similar analgesic effect as SCS, but it's possible that DRGS more easily evoke selective paresthesias over the distal painfully area through a more stable position in the epidural space. These facts could save energy, avoid displacement and necessity of electrodes replacement. DRGS is a promising strategy to treat CRPS pain, though today it has grade C of recommendation.

Spinal Cord Stimulation (SCS)

Even though the grade of recommendation is not a consensus (Grade B or C), SCS is the neuromodulation technique which has the best level of evidence as an effective intervention to treat refractory CRPS pain. According to this, a Cochrane systematic review and three others papers in the medical literature have concluded for limited evidence in quality and quantity [21,29,43,44]. Although the risks of death or critical complications with SCS were uncommon and low, undesirable occurrences were frequent and costs were considered high. In fact, these reviews have found a modest pain-relieving outcome with high rates of complications. Turner [44] estimated that about 34% a weighted average of patients who had the device permanently implanted had side effects or complications. The most frequent complications reported were: local contamination, systemic infections, pain at the site of the implants, need for reposition or replacement

of some devices' components, equipment failure and movements or cramps resulting from elevated amplitude.

Simpsom [45] assessing pain control and cost-effectiveness also found moderate evidence of SCS effectiveness (CRPS type I) at high costs. He reasoned that it is hard to calculate due to the high variability in device cost, longevity, complications and necessity of revisions or replacement of devices components.

Though many case series have reported positive effects of SCS, Kemler [24-26] has published the only high quality randomized controlled trial. Actually, it was reported in three papers that have assessed the six-month, two-year and five-year follow-up time. Despite the limited number of patients (n=36), open study characteristics and the randomization technique (2:1 ratio to receive SCS or SCS plus physical therapy); the conclusion generated the best quality of evidences available until now. Actually, the majority conclusions in the major meta-analyses and systematic reviews about SCS effectiveness on CRPS pain treatment were supported by it. In its final analyses, Kemler concluded that the pain-relieving effect decreased from device implantation to the third-year follow-up, when it was not significant. In addition, SCS has not significantly influenced quality of life scores and 42% of patients had complications which the most frequent was generator replacement. Assuming SCS is successful, an economic analysis demonstrated that it can be cost-effective and, even more economic than further treatments, in two years [26].

Despite of these critical analyses, this issue is far from consensus. Taylor [46] has considered SCS on CRPS pain treatment as grade A of recommendation though the studies included in his systematic review were almost the same which were cited above. According to that, Poree [28] does not consider SCS as final therapy, but he proposed to ponder that precociously in early stages as traditional interventions have been shown unsuccessful.

Motor Cortex Stimulation (MCS)

To date, there are few reports about CRPS patients treated with this technique though it seems to have significant effect on CRPS pain [47-50] and superior weighted responder rate than non-invasive techniques [51]. Even though MCS has high cost and higher complication rates (as well as other invasive stimulation technics), at this time it is more commonly employed than DBS, since it is more easily carried out and it has a large spectrum of indications [52]. Currently, there is no high-quality randomized trial assessing MCS to treat CRPS patients, although Fontaine [53] assessed its effectiveness and side effects on chronic neuropathic pain approach in a systematic review. After a year, some sort of pain improvement were observed in 45% of patients treated (n=152). The most frequent complications reported were infections (5.7%), device-related problems (5.1%) and seizures (12%) [53]. Based on available evidences, MSC is better graduated as grade C of recommendation to refractory CRPS patients.

Deep Brain Stimulation (DBS)

Several authors have reported their lasting successful pain relief with DBS to treat either nociceptive or neuropathic chronic pain, though different targets, surgical procedures and stimulation techniques have been complicating a critical and comparative analysis [54]. Generally speaking, periaqueductal gray (PAG) and periventricular gray (PVG) stimulation are recommended for the treatment of lasting nociceptive pain; whilst ventroposterolateral (VPL), ventroposteromedial thalamic nucleous (VPM) or internal capsule (IC) stimulation are advocated for neuropathic pain [55-63]. The absence of randomized controlled trial and high quality meta-analysis studies also makes it difficult to get a better perception of DBS usefulness in CRPS pain treatment. Bittar [64] published a meta-analysis assessing the efficacy of DBS in chronic pain treatment which has included six studies that had used PVG/PAG, VPL/VPM and IC as targets for long-term stimulation. Though it has found 47% lasting success when it was done to relieve pain from deafferentation (n=220), it cannot be generalized to treat CRPS since only five possible CRPS patients were enrolled among 424 patients treated. In addition, the cases included were very heterogeneous and the methods to assess pain and outcomes were not standardized [64]. In conclusion, DBS to treat CRPS pain would be better graduated as Grade C.

Conclusion

Although neuromodulation is an emerging approach that seems to be safe and efficient to treat chronic pain, its use in CRPS patients is far from consensus. In recent years, trials using neuromodulation have been increasing fast in both quantity and quality, although the quality of evidences and recommendation are still weak. In an overall attempt much of evidences come from case reports, retrospective case series or prospective studies with short follow-up and small number of patients. In addition, many of them lack methodology quality in terms of randomization, blinding, controls and pain assessments. It is extremely worse if we consider only invasive neuromodulation since a few prospective studies were open and improperly controlled. Also it is necessary to mention that many of them were sponsored by industries. The major meta-analysis and systematic reviews available for both strategies (invasive or not) are either limited in quantity or quality. Additionally, although many of them were performed using studies and casuistic in the same period of time; the conclusions were heterogeneous, inconsistent and discordant.

Future Prospects

High quality clinical trials using neuromodulation on CRPS chronic pain have been fast increasing, as well as technological advancement in neuromodulation. New emerging non-invasive techniques of neuromodulation have been reported with promising results such as dTMS [65], double or triple pulse TMS, RINCE stimulation and tDSC. Even though their capacity to influence has been reported, many properties of its effects on the cortical and deep circuitry are unknown. dTMS has

opened a perspective to test new targets in a non-invasively way such as the insula and other areas involved in many aspects of pain sensation as emotion, behavior and pain control. A further interesting aspect is that rTMS apparently can foresee the effect of epidural MCS; consequently its use would improve the selection of patients to this invasive procedure [66]. Regarding invasive techniques, it is hard to believe that a randomized multicentric controlled double-blinded study could be performed due to ethical and operational issues, but it seems to be an efficient approach based on prospective case-series reported. The appropriately chosen targets, or combinations of them, may remain as an important study object in the next years. It is very likely that two or more neuromodulation systems could have a synergic effect [50,67]. The same way that neurostimulator devices are becoming smaller, long-lasting and rechargeable, electrodes are also becoming easier to implant, with multiple contact lines available [68]. In addition, the software and options of stimulation are becoming very sophisticated and precise. Apart from these technological advancements, the business model and approach to neuromodulation need to shift radically. Instead of current low-volume and high-cost model, the disease-management solutions are demanding for practical, non-invasive and custom devices, at a low cost. Probably, for the next several years the best targets and techniques will be clear and new personal portable devices, implantable or not, will be available at a lower cost.

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