Complex Regional Pain Syndrome: A Quantitative Review of Current Treatments

Síndrome dolorosa regional complexa: Uma revisão quantitativa dos tratamentos atuais

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Abstract

Introduction Complex regional pain syndrome (CRPS) is a disease that causes intense pain mainly in the upper and lower limbs of the patients, impairing the quality of life of those affected by the syndrome. Its pathophysiology has not yet been fully discovered and described. Also, treatments need to advance in the search for pain relief in those affected by the disease. The present article aims to describe the pathophysiology of CRPS and, mainly, to quantitatively analyze the efficiency of new treatments against pain caused by the disease.

Methods Several articles on clinical trials described in a table were included in the present study, and a systematic review of the effectiveness of current treatments was performed.

Results A total of 29 articles from clinical trials were selected using the preselection criteria. Surgical treatments against CRPS had a 56.9% efficiency in reducing painful sensation, and conservative treatments against CRPS had a 40.82% efficiency in reducing pain sensation.

Conclusion Complex regional pain syndrome is a disease that causes pain in patients and worsens the quality of life of those affected by it. The treatments are diverse, and their efficiencies vary from bad to excellent.

Keywords
- complex regional pain syndromes
- neurosurgery
- therapeutics
- pathology

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Resumo

Introdução A síndrome dolorosa regional complexa (SDRC) é uma doença que causa dor intensa principalmente nos membros superiores e inferiores dos pacientes, prejudicando a qualidade de vida dos afetados pela síndrome. Sua fisiopatologia ainda não foi completamente descoberta e descrita. Ademais, tratamentos precisam avançar na busca do alívio da dor naqueles afetados pela doença. O objetivo do presente artigo é descrever a fisiopatologia da SDRC e, principalmente, analisar quantitativamente a eficiência dos novos tratamentos contra a dor causada pela doença.

Métodos Foram incluídos no presente estudo diversos artigos sobre ensaios clínicos descritos em uma tabela e foi feita uma revisão sistemática sobre a eficiência dos tratamentos atuais.

Resultados Foram selecionados 29 artigos de ensaios clínicos por meio do critério de pré-seleção. Tratamentos cirúrgicos contra a SDRC tiveram uma eficiência de 56,9% na redução da sensação dolorosa e os tratamentos conservadores contra a SDRC tiveram uma eficiência de 40,82% na redução da sensação dolorosa.

Conclusão A SDRC é uma doença que causa dor nos pacientes e piora da qualidade de vida dos afetados por ela. Os tratamentos são diversos e suas eficiências variam de ruim a excelente.

Palavras-chave
- síndrome da dor regional complexa
- neurocirurgia
- terapêutica
- patologia

Introduction

Complex regional pain syndrome (CRPS) is a disease that was discovered and described by Silas Weir Mitchell. The American doctor described this pathology when he realized that some patients who suffered gunshot wounds in the US secession war developed pain and hyperalgesia in the extremities of the limbs.[1]

This syndrome has been known by several names since its discovery. Known today as CRPS, names like post-traumatic pain syndrome, sudeck's atrophy, and reflex sympathetic dystrophy have already been used.[2]

Complex regional pain syndrome is classified into two different groups: type 1, the most common, is the one in which the patient does not have an identifiable nerve injury. This type was formerly known as "reflex sympathetic dystrophy"; and CRPS type 2, previously called "causalgia", is the one that presents a proven associated nerve injury.[2,3]

Based on the diagnosis from doctors in general, the incidence of CRPS is of 26.2/100,000 people per year. As for the diagnosis made and confirmed by specialists, this number decreased to 19.5/100,000, and with specialists who diagnose following the criteria of the International Association for the Study of Pain (IASP) we have a rate of 16.8/100,000 inhabitants.[4]

The incidence related to gender shows a big difference, with predominance in women. Men are 22.7% of those affected by the CRPS, while women are 77.3% of the patients. The upper extremities are 10% more affected than the lower ones, with no preference for laterality. Furthermore, the most common triggering factors are fractures and sprains, with fractures leading in percentage.[4]

The pathophysiology of CRPS is not yet fully understood, with only a few hypotheses that contribute to clarify the mechanism that causes this pathology. In the following paragraphs, the hypotheses most commonly related to CRPS are presented.

The main mechanisms that explain the pathophysiology of CRPS are nerve injury, ischemic reperfusion injury or oxidative stress, central sensitization, peripheral sensitization, altered sympathetic nervous system function or sympathetic-afferent coupling, inflammatory and immune-related factors, genetic factors, brain plasticity, and psychological factors.

Nerve Injury

Even though the pathophysiology of CRPS is not fully comprehended, it is known that persistent inflammation in the affected limb is something common in all patients affected by this condition. The phenomenon that explains the onset of this inflammation is a nerve injury, which in cases of CRPS type 2 has a clear and determined origin. In cases of CRPS type 1, however, this lesion cannot be explained, largely because the lesion was caused in small fibers, structures that often cannot be identified in imaging exams. About 90% of patients with CRPS do not have an identifiable nerve injury; thus, CRPS type 2 represents only 10% of the patients affected by this syndrome.[5,6]

Reperfusion Injury or Oxidative Stress

The mechanism of reperfusion ischemia is also pointed out as one of the factors that contribute to the development of CRPS type 1. Patients who experienced trauma and had to immobilize the injured limb after surgery were more likely to develop the syndrome.[7] The mechanism of reperfusion ischemia is already well-known. The process results in an accumulation of free radicals leading to oxidative stress. The oxygen supplied after reperfusion generates reactive oxygen species (ROS), a situation made possible by the lack of production of antioxidant agents by the ischemic tissue. Reactive oxygen species promote endothelial dysfunction and DNA damage, in addition to inflammation, which can lead to a cascade of cytokinins that will result in cell death

and symptoms related to the pathophysiology of the inflammatory process.[8,9] Studies that carried out ischemia experiments with consecutive reperfusion in rats showed that the animals triggered symptoms similar to those of SDRC type 1. Hyperalgesia and allodynia were observed even though no nerve damage was found in rodents.[10,11]

Central Sensitization

Sensitization of the central nervous system is also one of the hallmarks of complex regional pain syndrome. The lesion triggers the release of neurotrophic factors and proinflammatory substances, such as bradykinins and prostaglandins that, together, activate phosphokinases A and C, which in turn phosphorylate specific sodium channels of sensory neurons. This mechanism leads to peripheral sensitization of afferent nociceptors. This entire process of peripheral sensitization leads to continuous depolarization that will lead to a blockage of magnesium ions in NMDA receptors, the main receptor of the glutamatergic system located in the postsynaptic membrane of neurons. The blocking of magnesium ions causes these receptors to be activated, thus leading to depolarization of the pain pathway and amplifying its signal, finally causing central sensitization.[12]

Peripheral Sensitization

After a tissue injury to the peripheral, as to the central, nervous system provides a sensitization that protects the body against unnecessary movements. This sensitization in the peripheral nervous system occurs thanks to the increase in the firing rate of the nociceptors and its response to normally painful stimuli, with an antagonist decrease in the firing threshold for thermal and mechanical stimuli.[13–15] Inflammatory mediators such as proinflammatory cytokines (TNF-alpha, IL-1beta), prostaglandin E2 (PGE[2]) , bradykinin, and nerve growth factor (NGF) increase the sensitivity and excitability of nociceptors by enhancing the activity of pronociceptive receptors and ion channels.[13]

Moreover, a study developed by Moy et al. in 2017 demonstrates that phosphorylation of the 5′ cap-binding protein eIF4E by its specific mitogen-activated protein kinase (MAPK) interacting kinases (MNKs) 1/2 is a key factor in nociceptor sensitization and the development of chronic pain.[14] The authors, by these studies, advocate in favor of a new pain pathway of nociceptive plasticity; thus, it is clear that the pathophysiology of CRPS is, indeed, intriguing and multifactorial.

Altered Sympathetic Nervous System Function or Sympathetic–afferent Coupling

The medical literature also assumes that modifications in the sympathetic nervous system contribute to CRPS, which in the past was known as reflex sympathetic dystrophy. This information, nevertheless, is controversial, since a prospective study in patients early after fractures shows that those with reduced sympathetic outflow after the injury are at greatest risk of developing subsequent CRPS symptoms.[16]

Localized injuries have been shown to result in the expression of catecholamine receptors on nociceptive fibers, so the circulating catecholamines released after the stress and pain might directly increase the firing of nociceptors, a reflex known as sympathetic-afferent coupling, observed in various studies that hypothesized that this mechanism plays a role in the severity of the symptoms.[17–22] These, once again, demonstrate a multifactorial principle in the genesis of CRPS with the intersections of sympathetic and peripheral sensitization theories.

A common symptom of CRPS that is explained in part by the sympathetic system is the temperature asymmetry. Vasodilating drugs and sympathetic blockade have been cornerstones of therapy in cold CRPS for years. However, only a limited part of these patients improves on this kind of therapy. Research has shown a pivotal role for inflammation in the pathophysiology of CRPS,[23] which will be discussed below.

Inflammatory and Immune-related Factors

Here we will discuss what may be the latest and most complex mechanism involving CRPS.

This concept seems to link the many other mechanisms and to participate decisively in the elucidation of pathophysiology.

Evidence of the involvement of inflammatory mechanisms, especially in the acute phase, is present in studies documenting raised concentrations of proinflammatory neuropeptides and mediators, such as substance P, calcitonin gene-related peptide, bradykinin, and cytokines interleukin-1β (IL-1β), interleukin-2 (IL-2), and interleukin-6 (IL-6), tumor necrosis factor α (TNF- α) in the systemic circulation, cerebrospinal fluid, and affected limbs of patients with CRPS, which can explain the symptoms of vasodilation causing a warm red appearance in the affected area, and may increase hair growth and sweating.[24–37]

In humans, increased numbers of proinflammatory monocytes (CD14 + ; CD16 +) in addition to altered innate immune responses and mast cells have been reported in patients with CRPS compared with healthy controls.[38–41] A new theory advocates that antibodies from people with CRPS may be capable of transferring the condition to previously unaffected individuals, also supporting a role for immune mechanisms.[42] In a work by Goebel et al. from 2011, immunoglobulin G (IgG) from patients with CRPS when injected into mice in the absence of any injury induced motor changes, characteristic of CRPS.[43] This autoimmune model[44] can explain the link between the autonomic nervous system and the CRPS, since the presence of autoantibodies directed against β2 adrenergic and muscarinic type 2 receptors were found in patients with CRPS.[45–47]

Furthermore, a study with mice model conducted in 2019 demonstrated that, in CRPS, IgG is significantly increased and seems to prolong swelling and induce stable hyperalgesia. The author also says that CRPS IgG-injected mice displayed sustained microglia and astrocyte activation in the dorsal horn of the spinal cord and pain-related brain regions, indicating a link with central sensitization. Even more interesting, genetic deletion of interleukin-1 (IL-1) using IL-1αβ knockout mice and perioperative IL-1 receptor type 1 blockade with the drug anakinra prevented these changes,

showing one other possible correlation between various theories such as inflammatory, autoimmune, and genetics hypothesis to the CRPS pathophysiology.[48]

Although well explained, the autoimmune theory is not yet totally elucidated. One parallel, randomized, placebo-controlled, multicenter trial tried to confirm the efficacy of low-dose IVIg compared with placebo in reducing pain during 6 weeks in adult patients who had CRPS from 1 to 5 years but did not succeed, emphasizing once again the multifactorial genesis of CRPS.[49]

Brain Plasticity

Neuroimaging testing suggests that several brain changes are associated with CRPS.[50–54] Although recent studies point out that the change in the brain is associated with the onset of the syndrome, it is not known for sure if this is what occurs or if it is the syndrome that causes the change in the brain.[50] However, the longer you develop the syndrome, the greater the change in neuroplasticity.[53]

In CRPS, there is an asymmetry between the corresponding brain regions. A reduction (structure or function) occurs on the side of the affected brain or there is an increase on the side of the unaffected brain.[50]

The main brain areas where this difference in asymmetry occurs are endogenous pain inhibitory pathways (opioid-mediated), primary and secondary somatosensory cortices, the primary motor cortex, the insula, and the cingulate cortex.[50–54]

Genetic Factors

There is a lack of studies of genetic factors in CRPS. However, some family-based studies reported a potential genetic predisposition.[51] The studies have identified polymorphisms at the genes encoding α1a adrenoceptors and the human leukocyte antigen (HLA) system (HLA-DQ8, HLA-B62), tumor necrosis factor-alpha (TNFα) gene and the angiotensin-converting enzyme gene.[50,51] Due to the lack of studies on the genetic factors involved in CRPS, the pathophysiological mechanism related to genetics is still not completely understood.[52]

Psychological Factors

It is not known for certain whether psychological factors are directly related to the development of CRPS, but it is suspected that anxiety and depression are related to the syndrome.[50,51] It is suspected that psychological factors alone do not contribute to the onset of the syndrome; however, psychological factors linked to tissue damage may imply an increase in the severity of the syndrome, which might represent an increase in the intensity of the pain.[50,54] It is also suspected that psychological factors, especially before invasive procedures, provide an increase in the chance of developing CRPS.[50]

The main signs and symptoms found in patients with CRPS are spontaneous pain; hypoesthesia and hyperpathia; edema; skin blood flow abnormality; color change; abnormal sudomotor activity; tissue atrophy; and involuntary movements.[4,55]

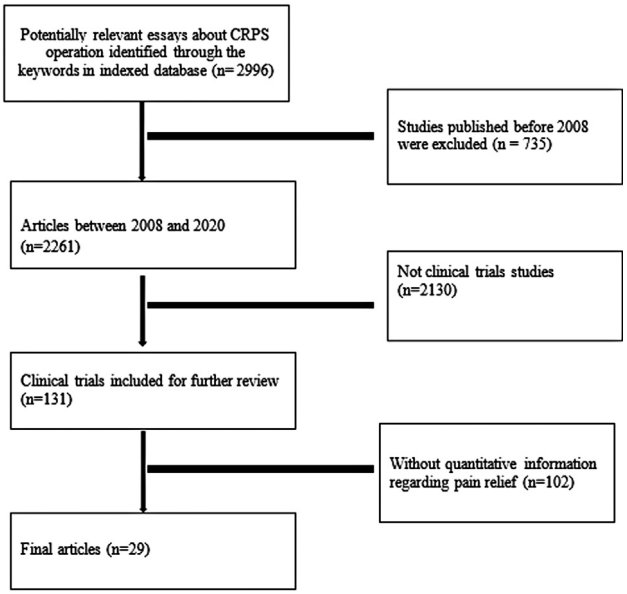

Fig. 1 Clinical trial inclusion criteria.

The diagnosis of CRPS is clinical, without imaging indicators or precise serum markers that indicate this pathology. The Budapest criteria is the one adopted to perform the diagnosis.[56]

The objective of the present systematic review is to show the results of the most recent unconventional treatments that add quality of life and improve the prognoses of CRPS patients.

Materials and Methods

To perform the systematic review, a broad review was conducted on the PubMed databases in the literature until September 2020. The search was initially performed with the keywords *complex regional pain syndrome*. A total of 2,996 articles were found in this search. Studies published before 2008, studies that were not clinical trial, and articles without quantitative information regarding pain relief were excluded. On this research, 29 results were obtained ►**Fig. 1**.

Results

►**Table 1** aimed to analyze how quantitatively the level of pain decreases in a given treatment against CRPS.

For that, we analyzed some initial quantitative mathematical quantities (average of pain, the median of pain, maximum pain) given by the articles in the baseline. We adopted these mathematical numbers as the initial average of the table at 100%.

Later, in the analysis of the article, with the quantitative number of the pain level given by the articles after the treatment (final average) of the last follow-up, we were able to arrive at how much the pain decreased in that particular treatment. This value was calculated by subtracting the final average multiplied by 100%, followed by dividing

Table 1 Description of Clinical Trials studies for CRPS treatment

REFERENCE	NUMBER OF PATIENTS (EFFECTIVE/CONTROL)	CRPS TYPE	TREATMENT	FOLLOW-UP (MONTHS)	PAIN RELIEF TREATMENT COMPARED WITH BASELINE	CONTROL PAIN RELIEF COMPARED WITH BASELINE (%)	CLASSIFICATION
[57]	54 (36/18)	1	spinal cord stimulation	60	25.37	14.28	fair
[58]	22 (22/0)	1	stellate ganglion blockade	0.5	87.5	–	excellent
[59]	13 (7/6)	1	low-dose intravenous immunoglobulin	0.83	25	12.5	fair
[60]	67 (33/34)	1	ct-guided radiofrequency neurolysis	24	67.6	21.2	good
[61]	42 (42/0)	1	intrathecal baclofen	12	22.4	–	bad
[62]	14 (14/0)	1	spinal cord stimulation	6	71.8	–	good
[63]	29 (15/14)	1	Ketamine	3	71.4	22.6	good
[64]	56 (29/27)	1	intravenous magnesium	3	14.8	10	bad
[65]	13 (6/7)	1	infliximabe	1.5	38	0	fair
[66]	74 (40/34)	1	amino-bisphosphonate neridronate	1.3	65.6	32.1	good
[67]	22 (12/10)	1	intramuscular magnesium sulphate	0.75	8.21	–	bad
[68]	29 (15/14)	1	thoracic sympathetic block	12	36	5.19	fair
[69]	51 (51/0)	1	spinal cord stimulation of the dorsal root ganglion	12	66.3	56.7	good
[70]	28 (14/14)	1	mirror therapy in stroke patients	6	50	–	good
[71]	53 (27/26)	1	pain exposure physical therapy	9	28.6	30.1	fair
[72]	29 (29/0)	1	oral corticosteroids	1.5	13.33	–	bad
[73]	52 (C.O.T.)	1	prednisolone	2	57.2	–	good
[74]	30 (15/15)	1	transcutaneous electrical nerve stimulation	UNK	70	–	excellent
[75]	33 (18/15)	1	exposure in vivo	6	49	47.5	fair
[76]	105 (55/50)	1 and 2	dorsal root ganglion stimulation	12	81.39	67.16	excellent
[77]	28 (C.O.T.)	1 and 2	spinal cord stimulation	2.5	45.24	12.37	fair
[49]	108 (56/52)	1 and 2	low-dose intravenous immunoglobulin treatment	1.5	6.76	3.5	bad
[78]	22 (11/11)	1	transcranial direct current stimulation	1.5	16.23	8.77	bad
[79]	9 (4/5)	1	mycophenolate treatment	5.5	45.45	–	fair
[80]	15 (C.O.T.)	UNK	paravertebral block performed at the t2 level	UNK	50.06	–	good
[81]	52 (26/26)	1	bioptron light therapy combined with conventional therapy	0.5	93.65	80.1	excellent
[82]	30 (15/15)	1	fluidotherapy combined with conventional therapy	0.75	50	37.5	good
[83]	12 (12/0)	1	short term glucocorticoid	0.2	50	–	good
[84]	24(12/12)	1 and 2	selective l4 dorsal root ganglion stimulation	3	37.72	–	fair

Abbreviations: C.O.T., crossed over treatment; CT, computed tomography; UNK, uninformed.

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it by the initial average, from 100%. It is worth mentioning that this analysis was performed in the effective therapy group (100% of the articles in the table) and the control when it presented quantitative data.

Furthermore, the number of patients in the table does not necessarily reflect the initial number, but rather the final present number described in each article. According to the quantitative data obtained in pain relief, we classified the treatment as bad, fair, good or excellent.

For the treatment to be considered bad it should reach a maximum of 24.9%, fair should be between 25 and 49.9%. To be evaluated as good, it should be between 50 and 74.9%, and for excellent, the range was from 75 to 100%.

Of the 29 articles that completed our selection criteria, 20.7% (6/29) of the performances of the treatments were bad, 31% (9/29) were fair, 34.5% (10/29) were good, and 13.8% (4/29) were excellent. The average painful reduction of all articles was 46.37% 7 months of follow-up (average).

Among these, surgical treatments (10/29) showed an average pain reduction of 56.9% and follow-up of 14.67 months; in contrast, conservative treatments (19/29) had a reduction of 40.82% and a follow-up of 3.16 months.

Moreover, the table shows an average of 38.48 patients in an average follow-up of 7 months. It is worth mentioning that the ratio between the average number of patients in the experimental group and in the control group is 1.52 (616/405, excluding crossed-over treatment).

Discussion

►**Table 1**

According to the data in ►**Table 1**, surgical treatments (10/29) showed an average pain reduction of 56.9% and a follow-up of 14.67 months. In contrast, conservative treatments (19/29) had a reduction of 40.82% and a follow-up of 3.16 months. Thus, we conclude that invasive treatments are more effective in combating one of the symptoms of CRPS: pain.

Among the surgical treatments, according to ►**Table 1**, in descending order, the procedures that most reduce pain are: stellate ganglion blockade, dorsal root ganglion stimulation, spinal cord stimulation,[62] computed tomography-guided radiofrequency neurolysis, spinal cord stimulation of the dorsal root ganglion, paravertebral block performed at the t2 level, spinal cord stimulation,[77] selective l4 dorsal root ganglion stimulation, thoracic sympathetic block, and spinal cord stimulation.

However, the most efficient treatment for pain reduction was a nonsurgical treatment, bioptron light therapy combined with conventional therapy.

Conclusion

Complex regional pain syndrome is a severe issue that affects the quality of life of the patients and interferes with one's well-being. This illness does not have a well-established pathophysiology; thus, the option of treatments is diverse in the literature. In the present study, we reviewed the literature to explain the possible treatments of CRPS. We conclude that surgical treatments are more efficient in decreasing pain in patients with CRPS. We suggest that further studies that analyze pain reduction in CRPS are needed.

Ethics Approval and Consent to Participate

The National Health Council of Brazil, by resolution 466/2012, exempts this type of study from the research ethics committee, since it is a transversal study and all data is available on the internet free of charge and anonymously.

Conflict of Interests

The authors have no conflict of interests to declare.

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