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Analytical Review of Complex Regional Pain Syndrome for Clinicians

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Abstract

A painful and incapacitating condition known as complex regional pain syndrome (CRPS) can develop following a stroke, an injury to the limbs, or occasionally even without any known precipitating event. There are two categories for CRPS: Patients with CRPS-I do not have a verified nerve injury, but those with CRPS-II have linked nerve damage. Different physiopathology can cause CRPS. Both peripheral and central mechanisms, including neuroplastic changes like cortical reorganization, altered afferent-efferent feedback, and central autonomic dysregulation, have been observed. Peripheral mechanisms include inflammation, peripheral sensitization, and sympatho-afferent coupling. Patients with CRPS types 1 and 2 may experience clinical symptoms and their severity in this situation differently. The Budapest Criteria stipulates that a patient must exhibit at least one symptom in two or more of the four categories of sensory, vasomotor, sudomotor/edema, and/or motor/trophic at the time of evaluation. Ketamine, memantine, intravenous immunoglobulin, epidural clonidine, intrathecal clonidine/baclofen/adenosine, aerobic exercise, mirror therapy, virtual body swapping, and dorsal root ganglion stimulation may all have therapeutic benefit. Experiments have also shown an increasing role for peripheral sympathetic nerve blocks, as well as lumbar/thoracic sympathetic, stellate ganglion, and brachial plexus blocks.

Keywords: Complex regional pain syndrome, Budapest, Ketamine, Vitamin C

Introduction

A painful and incapacitating condition known as complex regional pain syndrome (CRPS) can develop following a stroke, an injury to the limbs, or occasionally even without any known precipitating event. [1] There are two categories for CRPS: Patients with CRPS-I do not have a verified nerve injury, but those with CRPS-II have linked nerve damage [2]. Between 1 and 5% of patients with traumatic injury to an extremity [3] and up to 20% of patients with hemiparesis [4] are at risk for developing CRPS type 1. Different physiopathology can cause CRPS. Both peripheral and central mechanisms, including neuroplastic changes like cortical reorganization, altered afferent-efferent feedback, and central autonomic dysregulation, have been observed [5, 6]. Peripheral mechanisms include inflammation, peripheral sensitization, and sympatho-afferent coupling. Additionally, people with CRPS type 1 exhibit altered sensory-motor integration and distorted body perception, which result in a loss of function and symptoms that resemble cognitive, sensory, and motor neglect [5]. Severe hypoesthesia to mechanical stimuli and full fulfillment of the neuropathic pain criteria are two characteristics of CRPS type 2 [5]. Patients with CRPS types 1 and 2 may experience clinical symptoms and their severity in this situation differently. Budapest, Hungary hosted the international consensus gathering to examine the problems with CRPS diagnosis and make recommendations for changes to the IASP (International Association for the Study of Pain) standards. The Budapest Criteria, which is today the accepted diagnostic standard for the diagnosis of CRPS, were born out of this. The Budapest Criteria stipulates that a patient must exhibit at least one symptom in two or more of the four categories of sensory, vasomotor, sudomotor/edema, and/or motor/trophic at the time of evaluation [3], must report at least one symptom in all four of the aforementioned categories [4], there is no other diagnosis that better explains the patient's signs and symptoms [7]. Allodynia and/or claims of hyperesthesia are examples of sensory symptoms.

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Vasomotor symptoms include reports of, or the existence of, temperature asymmetries, as well as changes in or asymmetries in skin tone. Symptoms of sudomotor/edema include reports of edema, its presence, changes in sweating, and asymmetry in sweating. Reduced range of motion, motor dysfunction (weakness, tremor, dystonia), and/or trophic alterations are some examples of motor/trophic symptoms (hair, nail, skin) [7].

Objective

This updated review's main goal is to offer a critical evaluation of the most recent research on the treatment of CRPS that has come from published Randomized Controlled Trials.

The various treatment modalities emergent from the RCT of recent systematic reviews are listed below.

Various treatment modalities

Ketamine, memantine, intravenous immunoglobulin, epidural clonidine, intrathecal clonidine/baclofen/adenosine, aerobic exercise, mirror therapy, virtual body swapping, and dorsal root ganglion stimulation may all have therapeutic benefit. Experiments have also shown an increasing role for peripheral sympathetic nerve blocks, as well as lumbar/thoracic sympathetic, stellate ganglion, and brachial plexus blocks [8]. Patients with CRPS type 1 may experience pain relief after Graded Motor Imagery and Mirror Therapy [9].

Pharmacological agents

1. Ketamine

Ketamine infusion is used for the treatment of CRPS, the dosage ranged from 0.15 mg/kg to 7 mg/kg. Ketamine infusion led to a reduction in pain scores and symptom alleviation. Treatment-resistant CRPS patients who received ketamine infusions reported adequate pain reduction. This shows that individuals who have not experienced any meaningful pain reduction from conventional conservative treatments may find ketamine infusion to be an effective method of treatment [10].

2. Glucocorticoids

There were several different ways to provide glucocorticoids, with oral being the most popular one. Clinical symptoms, pain alleviation, and range of motion were among the outcome characteristics that showed the most variation, according to van den Berg C et al 11. In all but two investigations, the use of glucocorticoids resulted in an improvement in the parameters. Improvements in both pain management and range of motion were seen in particular. It seems that using glucocorticoids for CRPS for longer than three months is less effective [11]. In their investigation, the authors covered a vast range of glucocorticoid delivery techniques. Uncertainty persists regarding the best dosage and manner of delivery. Since the pathogenesis of CRPS is still partially understood, future research should include an intervention study as well as investigations into the underlying causes and the most effective treatment.

3. Prednisolone

Prednisolone used orally is a successful treatment for CRPS symptoms. Furthermore, although oral prednisolone doses of 30-100 mg/day were initially used in these investigations, it was discovered that 30 mg/day was as useful for managing the symptoms by Kwak SG [12]. Prednisolone was equally as effective when used for 1-2 weeks as it was when used for 1-3 months. Additionally, only 0%–30% of the participants in these studies experienced minimal adverse effects from prednisolone [12].

4. Immunomdulators

There is strong evidence that the pathophysiology of CRPS is heavily influenced by inflammation. By working on the inflammation's mediators, immunomodulation drugs lessen the symptoms of inflammation. Dirckx M et al [13] conducted a review on different immunomodulators like Glucocorticoids, TNF alpha antagonists, Thalidomide, and Bisphosphonates. As a result, the authors concluded that immunomodulation medications may be helpful for CRPS sufferers since inflammation plays a role in the pathogenesis of the condition. The use of immunomodulation medications, in theory, might reduce chronic inflammation, which might be a crucial step toward healing a crippled hand or foot and advancing rehabilitation [13].

5. Gabapentin

Some persons with post-herpetic neuralgia and peripheral diabetic neuropathy may get good levels of pain relief using gabapentin at doses of 1800 mg to 3600 mg daily. There is relatively little evidence for additional neuropathic pain categories. Patients view a reduction in pain intensity of at least 50% as a useful treatment result, and achieving this level of pain relief is linked to significant positive impacts on depression, exhaustion, and sleep disturbances, as well as the quality of life, function, and employment. With gabapentin, approximately 3 or 4 out of 10 patients experienced this level of pain reduction, as opposed to 1 or 2 out of 10 with a placebo. More than half of patients taking gabapentin will not get meaningful pain alleviation but may experience negative side effects. Since this review's last update [14], the conclusions have not changed.

6. Vitamin C

The duration of each study of vitamin C treatment was 42 to 50 days after accident or surgical fixation. According to effect sizes, vitamin C was associated with lower CRPS-1 rates than placebo (odds ratio 0.33, 95% confidence interval [0.17, 0.63]). Complications (odds ratio 1.90, 95% CI [0.99, 3.65]), functional outcomes (mean difference 6.37, 95% CI [-1.40, 14.15]), and pain scores (mean difference -0.14, 95%) [-1.07, 0.79]), there was no discernible difference between vitamin C and placebo. Overall, vitamin C was associated with lower CRPS-I rates than placebo, but without significant differences in complications, functional outcome, and pain levels. These results remain valid when stratified by fracture type (distal radius, ankle and foot surgery) and vitamin C dose (500 mg or 1 g) [15]. After orthopedic or trauma treatment, vitamin C should be used for 45-50 days as a preventive measure to avoid CRPS-I. Only one study found no difference in vitamin C supplementation with respect to prevention of CRPS-I. It can delay the onset of CRPS-I in orthopedic surgery [16].

7. Bisphosphonate and ketamine

When compared to placebo or reference medication,

bisphosphonate treatment significantly reduced pain scores as measured by the Visual Analog Scale/Numerical Rating Scale. The VAS/NRS values for pain were decreased as a result of ketamine therapy. Fassio A et al [17] back up the suggestion that parenteral bisphosphonates be used as the initial treatment for CRPS-I [17].

Other therapy

1. Physical, cognitive behavioral, and pharmaceutical therapy: Vescio A et al [18] emphasized physical therapy (PT), which is connected to cognitive behavioral therapy (CBT) and pharmaceutical therapy (PhT). Although it has been proposed that the combination of PT and CBT is the most effective, no standard procedure has been created. Pharmacological treatment should only be used on certain, refractory patients. It is highly recommended that a standard protocol be created. Mbizvo GK et al[19] found no indication of placebo analgesia in their meta-analysis of placebo responses in randomized controlled trials in patients with long-standing CRPS, published from 1966 to 2013.

Conclusion

The restoration of normal limb function is the aim of CRPS treatment. Although no one method has been demonstrated to prevent CRPS after surgery, avoiding prolonged immobilization may be crucial. As a result, it's crucial to start postoperative rehabilitation as soon as feasible. Above all, the goals of physical and occupational therapy are met with combination pharmacotherapy since it offers pain relief to assist physical rehabilitation, thus a multidisciplinary approach would seem to be ideal. For the majority of CRPS treatments, there is a severe dearth of high-quality evidence supporting their efficacy. It will continue to be challenging to develop an evidence-based strategy for managing CRPS until further extensive trials are conducted.

SYSTEMATIC REVIEW	FINDINGS OF THE STUDY
1. Méndez-Rebolledo G, Gatica-Rojas V, Torres-Cueco R, Albornoz-Verdugo M, Guzmán-Muñoz E. Update on the effects of graded motor imagery and mirror therapy on complex regional pain syndrome type 1: A systematic review. J Back Musculoskelet Rehabil. 2017;30(3): 441-449.	GMI and MT can improve pain in patients with CRPS type 1; however, there is not sufficient evidence to recommend these therapies over other treatments given the small size and heterogeneity of the studied population
2. Chitneni A, Patil A, Dalal S, Ghorayeb JH, Pham YN, Grigoropoulos G. Use of Ketamine Infusions for Treatment of Complex Regional Pain Syndrome: A Systematic Review. Cureus . 2021;13(10):e18910.	Ketamine infusion may be a useful form of treatment for patients with no significant pain relief with other conservative measures.
3. Kwak SG, Choo YJ, Chang MC. Effectiveness of prednisolone in complex regional pain syndrome treatment: A systematic narrative review Pain Pract 2022;22(3):381-390. . .	30-100 mg/day of oral prednisolone was initially administered in these studies, 30 mg/day was also found to be effective in controlling the symptoms. Although prednisolone was usually administered for 1-3 months, short-term treatment for 1-2 weeks was also reportedly effective.
4. Seth I, Bulloch G, Seth N, et al. Effect of Perioperative Vitamin C on the Incidence of Complex Regional Pain Syndrome: A Systematic Review and Meta-Analysis. J Foot Ankle Surg . 2022;61(4):748-754.	Vitamin C was associated with a decreased rate of CRPS- I than placebo, while no significant difference was found regarding complications, functional outcomes, and pain scores. These results hold true when stratifying fracture type (distal radius, ankle, and foot surgeries) and vitamin C dose (500 mg or 1 g).
5. Fassio A, Mantovani A, Gatti D, et al. Pharmacological treatment in adult patients with CRPS-I: a systematic review and meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2022;61(9): 3534-3546.	Bisphosphonates showed a significant reduction of the values of the VAS/NRS pain scale compared with placebo or reference therapy. Treatment with ketamine also documented a reduction in the values of the VAS/NRS pain scale. Treatment with other agents did not improve the values of the VAS/NRS pain scale.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his/her consent for his/her images and other clinical information to be reported in the Journal. The patient understands that his/her name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

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