Algorithm for multimodal medication therapy in patients with complex regional pain syndrome

Min Cheol Chang¹, Donghwi Park²

¹Department of Physical Medicine and Rehabilitation, Yeungnam University College of Medicine, Daegu, Korea
²Department of Rehabilitation Medicine, Daegu Fatima Hospital, Daegu, Korea

Complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy and causalgia, is a clinical entity characterized by classic neuropathic pain, autonomic involvement, motor symptoms, and trophic changes in the skin, nails, and hair. Although various therapeutic modalities are used to control CRPS-related pain, severe pain due to CRPS often persists and progresses to the chronic phase. In this study, we constructed an algorithm for multimodal medication therapy for CRPS based on the established pathology of CRPS. Oral steroid pulse therapy is recommended for initial pain management in patients with CRPS. Oral steroid therapy can reduce peripheral and central neuroinflammation, contributing to the development of neuropathic pain during the acute and chronic phases. If steroid pulse therapy offers poor relief or is ineffective, treatment to control central sensitization in the chronic phase should be initiated. If pain persists despite all drug adjustments, ketamine with midazolam 2 mg before and after ketamine injection can be administered intravenously to inhibit the N-methyl D-aspartate receptor. If this treatment fails to achieve sufficient efficacy, intravenous lidocaine can be administered for 2 weeks. We hope that our proposed drug treatment algorithm to control CRPS pain will help clinicians appropriately treat patients with CRPS. Further clinical studies assessing patients with CRPS are warranted to establish this treatment algorithm in clinical practice.

Keywords: Complex regional pain syndromes; Multimodal; Neuropathic pain; Reflex sympathetic dystrophy

Introduction

Complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy, causalgia, or shoulder-hand syndrome, is a clinical entity characterized by classic neuropathic pain, autonomic involvement, motor symptoms, and trophic changes in the skin, nails, and hair. Various therapeutic modalities such as physical techniques, exercise therapy, procedures, medication, and spinal cord stimulators have been employed to control CRPS-related pain. Despite these treatment strategies, severe pain caused by CRPS often persists and progresses to the chronic phase. Based on the established pathology of CRPS, we constructed an algorithm for multimodal medication therapy in CRPS, including the medication dose and sequence of administration.

Algorithm for multimodal medication therapy

To manage pain caused by CRPS, the diagnosis should be confirmed in accordance with the Budapest criteria. Oral steroid pulse therapy is recommended for initial pain management in patients with CRPS (Fig. 1). Oral steroid therapy can reduce peripheral...
CRPS diagnosed by the Budapest criteria

First steroid pulse treatment (initial dose prednisolone 1 mg/kg, and tapering 10 mg every other day for 2 wk)

Yes

Effective?

No

Second steroid pulse treatment

Effective?

No

Start medication for managing central sensitization
1. Start one medication at a time and maintain for at least 2–3 days to see if the drug is working
2. If the medication is effective, increase the dose and add the next medication
3. If the medication does not work, remove the drug and start the next one

Yes

Third steroid pulse treatment

Start medication for managing central sensitization

A. Medications for reducing glutamate secretion at the presynaptic membrane
1. Ca²⁺ channel blocker: gabapentin or pregabalin
2. Na⁺ channel blocker: lamotrigine, carbamazepine
3. γ-aminobutyric acid type A (GABAA) receptor: clonazepam
4. γ-aminobutyric acid type B (GABAB) receptor: baclofen
5. Alpha-adrenergic receptor: tizanidine
6. Serotonin, norepinephrine, dopamine: SNRI, dopamine agonist (ropinirole, pramipexole)

B. Medication for blocking AMPA receptors at the postsynaptic membrane
1. AMPA receptor blocker: perampanel

C. Medications for blocking μ-opioid receptors at the presynaptic membrane
1. Tramadol
2. Acetaminophen/tramadol
3. Oxycodone (not exceeding a total of 20 mg/day)
   Oxycodone immediate-release: for controlling sudden onset intermittent pain
4. Fentanyl patch or buprenorphine patch

Is pain well-controlled?

No

IV medication for blocking NMDA receptors at the postsynaptic membrane
1. Ketamine IV treatment for 10 days (3 mo interval)

Is pain well-controlled?

Yes

Maintain medication

No

IV medication for blocking Na⁺ receptors at the postsynaptic membrane
1. Lidocaine IV treatment for 10 days (3 mo interval)

Fig. 1. Algorithm of multimodal medication therapy in patients with complex regional pain syndrome. CRPS, complex regional pain syndrome; SNRI, serotonin–norepinephrine reuptake inhibitor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; IV, intravenous; NMDA, N-methyl-D-aspartate.
and central neuroinflammation, which contribute to the development of neuropathic pain during the acute and chronic phases [1]. Considering the dosage regimen, 1 mg/kg prednisolone acetate (maximum dose, 60–80 mg/day) should be prescribed as the initial dose, which is subsequently tapered to 10 mg every other day for 2 weeks [2]. If pain relief is achieved, a second cycle of prednisolone can be administered immediately, and a third cycle can be considered if the second cycle is more effective than the first. However, long-term prednisolone therapy is not recommended due to the well-known side effects of steroidal agents.

If steroid pulse therapy offers poor relief or is ineffective, treatment to control central sensitization in the chronic phase should be initiated. The basic mechanism of central sensitization involves glutamate secretion from the terminals of the spinal dorsal horn and primary sensory neurons and the response of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to the secreted glutamate [3]. In addition, sustained release of glutamate can cause trafficking of AMPA receptor subunits in the dorsal horn of the spinal cord. Such changes contribute to hypersensitivity, which underlies persistent pain [4].

Accordingly, the therapeutic goal is to reduce glutamate secretion from the presynaptic membrane or decrease glutamate binding to AMPA and NMDA receptors in the postsynaptic membrane [5,6]. Blocking or inhibiting Ca$^{2+}$, γ-aminobutyric acid (GABA), alpha-adrenergic, and Na$^+$-mediated receptors can reduce glutamate secretion by primary sensory neurons. In addition, enhanced serotonin, dopamine, and norepinephrine secretion by synaptic interneurons can facilitate reduced glutamate secretion [3]. Gabapentinoids (pregabalin and gabapentin) are Ca$^{2+}$ receptor ligands [7], whereas GABA receptor agonists include baclofen (GABA$_B$ receptor), clonazepam (GABAA receptor), and diazepam (GABA$_A$ receptor) [8]. Tizanidine and mirtazapine are alpha-2 adrenergic receptor agonists [9,10], while carbamazepine and lamotrigine are Na$^+$ blockers [11]. In addition, selective serotonin reuptake inhibitors (fluoxetine and escitalopram), serotonin and norepinephrine reuptake inhibitors (venlafaxine and duloxetine), tricyclic antidepressants (amitriptyline), mirtazapine (enhanced secretion of serotonin and norepinephrine), and dopaminergic agonists (ropinirole and pramipexole) can increase serotonin, norepinephrine, and dopamine in the synapse [12-14]. Perampanel can be used to block AMPA receptors in the postsynaptic membrane of the spinal cord dorsal horn [5]. If intolerable pain persists despite taking these drugs, appropriate doses of μ-opioid receptor agonists, such as tramadol (or acetaminophen/tramadol) or narcotics (e.g., oxycodone and tapentadol), should be considered.

Instead of starting two or more medications concurrently, it is recommended to administer one medication for at least 2 to 3 days to determine efficacy. If the medication is effective, the dose is increased, and the next medication is added. If the medication is ineffective, it is stopped, and the next medication is started.

If pain persists despite all drug adjustments, ketamine (maximum dose of 0.35 mg/kg/hour; day 1, 50% of maximum ketamine dose with 500-mL normal saline [N/S] for 4 hours; day 2, 75% of maximum ketamine dose with 500-mL N/S for 4 hours; days 3–5, maximum ketamine dose with 500-mL N/S for 4 hours; days 6–7, no administration; days 8–13, maximum ketamine dose with 500-mL N/S for 4 hours) with midazolam 2 mg before and after ketamine injection can be administered intravenously to inhibit the NMDA receptor [15]. Given that patients may experience resistance to ketamine therapy, an interval of at least 3 months is recommended after treatment. If this treatment fails to afford sufficient efficacy, intravenous lidocaine can also be considered for 2 weeks (day 1, 1 mg/kg lidocaine with 500-mL N/S for 4 hours; day 2, 2 mg/kg lidocaine with 500-mL N/S for 4 hours; days 3–5, 5 mg/kg lidocaine with 500-mL N/S for 4 hours; days 6–7, no administration; days 8–13, 5-mg/kg lidocaine with 500-mL N/S for 4 hours) [16].

**Conclusion**

We hope that our proposed drug treatment algorithm to control CRPS pain will help clinicians appropriately treat patients with CRPS. However, as this proposed protocol has no supporting evidence, further studies targeting patients with CRPS are needed to evaluate its effectiveness. Moreover, since several studies on calcitonin, bisphosphonate, and botulinum toxin injection have been reported, we believe that the CRPS treatment algorithm should be continuously updated through many studies in the future [2,17,18].

**Notes**

**Conflicts of interest**

Min Cheol Chang has been Associate Editor of *Journal of Yeungnam Medical Science* since 2021. He was not involved in the review process of this manuscript. There are no other conflicts of interest to declare.

**Funding**

None.

https://doi.org/10.12701/jyms.2023.00360
Author contributions
Conceptualization: all authors; Writing-original draft: all authors; Writing-review & editing: all authors.

ORCID
Min Cheol Chang, https://orcid.org/0000-0002-7629-7213
Donghwi Park, https://orcid.org/0000-0002-7724-4682

References