

# **IMPROVING OUTCOMES OF THERAPY-RESISTANT COMPLEX REGIONAL PAIN SYNDROME UTILIZING KETAMINE INFUSIONS AND COMPREHENSIVE REHABILITATION FOLLOWING AMPUTATION: A CASE REPORT**

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**Background:** Complex regional pain syndrome (CRPS) is a term describing signs and symptoms of a poorly understood neuropathic pain condition. Despite a number of treatment options, patients with CRPS often suffer from significant impairment and unsatisfactory pain relief. An option rarely considered in managing this condition is amputation due to concerns of pain recurrence or disease progression.

**Case Report:** A 50-year-old man with a history of refractory CRPS on high-dose opioids (over 400 morphine daily equivalents) presented with a request to consider amputation. After extensive interdisciplinary discussion, it was decided to proceed with amputation resulting in successful resolution of his CRPS symptoms with aggressive peri- and postoperative ketamine infusions and a comprehensive therapy program. The patient is now 6 years post amputation and denies phantom limb pain or the spread of CRPS to other limbs. He was subsequently tapered off all opioid medication and has only needed the occasional acetaminophen for pain.

**Conclusions:** We demonstrate the potential for a selective treatment approach in a patient with treatment-resistant CRPS using IV ketamine infusions.

**Key words:** Amputation, chronic pain, complex regional pain syndrome, ketamine

## **BACKGROUND**

Complex regional pain syndrome (CRPS) is a term describing a variety of debilitating chronic pain symptoms (1). The International Association for the Study of Pain (IASP) outlines criteria for CRPS with pain as a key feature (2). Criteria fall into 4 categories: sensory, vasomotor, sudomotor, and motor/trophic changes. Pain is disproportionate to any inciting event and there is no other explanation for the patient's symptoms. CRPS-I indicates the absence of peripheral nerve injury and

represents the majority of cases, and CRPS-II indicates the presence of peripheral nerve injury (3).

Treatment for CRPS includes kinesiotherapy, opioids and non-opioid medications, sympathetic nerve blocks, sympathectomy, and neuromodulation; however, evidence for their effectiveness is limited (4,5). Amputation of the affected limb is a rare, but potential end-stage treatment for patients who fail conventional modalities, with a small number of studies demonstrating that amputation does not improve patient outcomes and

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could worsen symptoms (6,7). Despite this, several published reports have demonstrated amputation as a reasonable treatment in therapy-resistant CRPS (7,8). There is also an increasing amount of evidence supporting ketamine for CRPS, related to antagonistic effects on N-methyl-D-aspartate (NMDA) receptors (9-14). The NMDA receptor is believed to play a major role in the wind-up phenomenon and central sensitization, both believed to be responsible for CRPS/neuropathic pain (12,15-18). Here, we present a successful case utilizing ketamine infusions before and after amputation, along with various modalities to improve pain, functionality, and to improve outcomes in a patient with treatment-resistant CRPS.

## **CASE**

A 50-year-old service member suffered a fall while on active duty within the US military, injuring his right knee. The patient experienced several years of locking and swelling and subsequently underwent arthroscopic surgery during which profound synovitis was noted, without identifiable arthroscopic findings or internal derangements that could explain the patient's symptoms. Due to persistent pain, he was referred to the chronic pain clinic at a Veterans Affairs medical center for further evaluation. His physical examination was significant for crusting, scaling, and discoloration of the right foot to the midhigh. He also demonstrated profound weakness, erythema, atrophy, and allodynia of the entire extremity.

For the next 17 years, the patient was managed with a variety of neuropathic medications, interventional procedures, and multidisciplinary therapies. This included kinesiotherapy biofeedback, lumbar sympathetic nerve blocks and sympathectomies, spinal anesthesia blockades, and a spinal cord stimulator trial. In addition, the patient was managed with opioids, including rotation of morphine, hydrocodone, fentanyl patch, hydromorphone, and methadone. None of these modalities provided him clinically significant pain relief.

Despite multimodal and multidisciplinary pain care, the patient's pain significantly affected his quality of life and resulted in the development of additional comorbidities. He developed metabolic syndrome, type-II diabetes mellitus, disuse atrophy of the lower extremities, and knee extension contractures from lack of movement. He also sustained several falls resulting in fractures of the femoral neck and distal tibia and fibula, and developed ichthyosis vulgaris lesions and

chronic skin infections requiring prolonged antibiotic therapy. He could only tolerate contracture and wound care while receiving spinal anesthesia, which became progressively difficult due to dural fibrosis. Furthermore, he was diagnosed with major depressive disorder, reporting hopelessness, frustration, and anger due to his decline in functional ability and wheelchair dependence. These factors resulted in further social isolation and culminated in a suicide attempt after over a decade of failed treatments.

An additional concern was the patient's high dose of opioids, which exceeded 400 morphine milligram equivalents (MME) per day. In order to taper down his daily opioid dose, regularly scheduled ketamine infusions were performed, infusing 320 mg ketamine over 4 hours and receiving 10 infusions over one year. The infusions helped the patient taper down to 28 MME, but despite this, the patient's pain persisted, and he continued to experience functional decline.

The patient expressed interest in amputation during his treatment, but citing limited evidence for amputation, the medical team did not initially consider this option. However, with his falls, contractures, functional decline, worsening comorbidities, and the dangers of high-dose opioids, amputation became a consideration of last resort.

Following psychological evaluation and interdisciplinary team discussion with Pain Management, Orthopedics, and Anesthesia regarding the goals of treatment, with a focus on function and quality of life, the patient underwent perioperative ketamine infusions to reduce pain sensitivity. After a series of titrated ketamine infusions, his CRPS symptoms were controlled sufficiently that the team felt he would be able to tolerate amputation. He then underwent above-the-knee amputation 11 days after his final ketamine infusion and immediately began an aggressive regimen of kinesiotherapy 5 to 7 times weekly in the acute rehabilitation unit consisting of transfers, stretching, strengthening, and contracture prevention. Upon discharge, he was titrated back to his 28 MME regimen.

His outpatient postoperative course was significant for immediate improvement in pain. He was given 2 postoperative ketamine infusions within one month of surgery, first receiving 320 mg of ketamine over 4 hours, and 10 days later receiving 360 mg over 4 hours, noting significant pain relief with each infusion. He was subsequently tapered off all opioid medication, reporting only occasional acetaminophen use. His

physical therapists noted a profound improvement in his mood, citing his sense of pride in his postamputation physical accomplishments as he improved in his outcome measures following amputation (Table 1). The patient is now 6 years post amputation and denies phantom limb pain or the spread of CRPS to other limbs. He continues to adjust to his daily demands both at home and in the community.

## DISCUSSION

When considering treatment options for CRPS, symptom management is the primary focus (19). Without resolution, CRPS may culminate in severe pain, contractures, osteoporosis, and reduced activities of daily living. Evidence-based guidelines regarding amputation in patients with CRPS-I state that there is insufficient evidence that amputation improves patient outcomes (20); however, the literature informing these guidelines has several shortcomings (21,22). First, studies reviewing amputation for the treatment of therapy-resistant CRPS-I did not use strict criteria for defining CRPS-I, such as those outlined by IASP, calling into question the number of patients who truly had CRPS (22). Second, a study by Dielissen et al (23) strongly influences the literature with report of a 100% recurrence rate of CRPS following amputation; however, this study allowed a diagnosis of CRPS in the absence of pain. This omission is critical, as CRPS-I is a pain syndrome. When posthoc analysis excluded data from the Dielissen et al study, only 8% of 37 patients had a recurrence of CRPS-I in amputated limbs. Pain was cited as a primary reason in 80% of amputations in CRPS-I, but no studies reviewed by Bodde et al (22) reported patient satisfaction related to level of pain following amputation. Third, overall patient satisfaction and changes in quality of life were so fragmented in these published reports that no conclusions could be drawn regarding the effect of amputation. Fourth, phantom pain is often cited as a reason to avoid amputation in CRPS treatment guidelines, but there is inconclusive data in the literature to validate this statement. Bodde et al reported a prevalence of 41% in studies that mentioned phantom limb pain after amputation, but prevalence ranged from 9% to 85% (22,24-26). Most studies did not include frequency of occurrence and the extent of resulting impairment. Therefore, given this variability, the frequency of CRPS-related complications following amputation is unclear.

Table 1. Functional measures of activity using locomotor capabilities index (LCI), advanced LCI, timed-up-and-go (TUG) and 2-minute walk test (2 MWT). Preamputation values were obtained using a front-wheel walker, and the postamputation values were obtained with a single point cane.

Functional Measure	Preamputation	Post Amputation
LCI	23 of 56	42 of 56
TUG	42 s	19 s
2 MWT	148 ft	292 ft

In addition to the shortcomings of the guidelines, several case reports and studies demonstrate amputation's potential in therapy-resistant CRPS (7,21). One review evaluating 21 patients with therapy-resistant CRPS who had undergone amputation noted that 95% of patients reported an improvement in some aspect of their lives (i.e., sleep, mood, physical appearance), 90% reported a reduction in pain, and 81% reported an improvement in mobility (6). Another study of patients with therapy-resistant CRPS followed 19 patients who underwent amputation; these patients reported better outcomes on multiple pain and mood scales when compared to controls who did not undergo amputation. Evidence also suggests that amputees had greater satisfaction with results when they themselves initiated the request for amputation, and overall satisfaction with results was closely related to how amputation results fit with preamputation expectations (22,27).

We only identified one other case report discussing ketamine infusions prior to amputation (7). That report describes the case of a 38-year-old man with therapy-resistant CRPS who underwent a ketamine infusion one week prior to below-the-knee amputation. At the 6-week follow-up, he reported pain scores of 3 to 4 of 10, down from 8 to 10 of 10. There are several important considerations explaining the success of this case. First, the patient initiated the discussion of amputation as a therapeutic option and all members of his multidisciplinary team were included in the final decision. Second, the patient received ketamine infusions that were slowly titrated over several months to an individualized dose to control the patient's symptoms. Third, amputation was offered to improve functionality, not to improve pain. Fourth, the patient's postamputation care was governed by functional rehabilitation, with ketamine infusions providing adjuvant treatment. With his pain well-controlled, the patient was able to focus on improving functionality.

## CONCLUSION

This case demonstrates that amputation may be a feasible treatment in therapy-resistant CRPS, especially when the patient has maximized all alternative treatments and is both functionally and socially isolated. By utilizing individualized pre- and postamputation ketamine infusions, combined with a comprehensive and interdisciplinary rehabilitation approach, our patient obtained relief after failing customary treatment. Although amputation correctly remains a treatment of last resort, this case demonstrates an alternative approach to treating refractory CRPS.

## Author Contributions

ID contributed to compiling data to write this report, wrote parts of the manuscript and contributed with editing. RM is the corresponding and submitting author, wrote parts of the manuscript (made the table), and contributed to editing. EP wrote parts of the manuscript and contributed to editing. MZ wrote parts of the manuscript and contributed to editing. SP wrote parts of the manuscript and contributed to editing.

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