CASE REPORT

# Complete Recovery From Intractable Complex Regional Pain Syndrome, CRPS-Type I, Following Anesthetic Ketamine and Midazolam

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■ **Abstract**

*Objective:* To describe the treatment of an intractable complex regional pain syndrome I (CRPS-I) patient with anesthetic doses of ketamine supplemented with midazolam.

*Methods:* A patient presented with a rapidly progressing contiguous spread of CRPS from a severe ligamentous wrist injury. Standard pharmacological and interventional therapy successively failed to halt the spread of CRPS from the wrist to the entire right arm. Her pain was unmanageable with all standard therapy. As a last treatment option, the patient was transferred to the intensive care unit and treated on a compassionate care basis with anesthetic doses of ketamine in gradually increasing (3–5 mg/kg/h) doses in conjunction with midazolam over a period of 5 days.

*Results:* On the second day of the ketamine and midazolam infusion, edema, and discoloration began to resolve and increased spontaneous movement was noted. On day 6, symptoms completely resolved and infusions were tapered. The patient emerged from anesthesia completely free of pain and associated CRPS signs and symptoms. The patient has maintained this complete remission from CRPS for 8 years now.

*Conclusions:* In a patient with severe spreading and refractory CRPS, a complete and long-term remission from CRPS has been obtained utilizing ketamine and midazolam in anesthetic doses. This intensive care procedure has very serious risks but no severe complications occurred. The psychiatric side effects of ketamine were successfully managed with the concomitant use of midazolam and resolved within 1 month of treatment.

This case report illustrates the effectiveness and safety of high-dose ketamine in a patient with generalized, refractory CRPS. ■

**Key Words:** central sensitization, complex regional pain syndrome, reflex sympathetic dystrophy, ketamine, NMDA-receptor

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## INTRODUCTION

The pathophysiology underlying complex regional pain syndrome I (CRPS-I) is incompletely understood but CRPS has recently been posited to be a disease of the peripheral and central nervous system.[1,2] In early stages of the disease, nociceptive input may be maintained by increased sympathetic activity.[3] A prolonged intense afferent barrage at the site of injury may initiate functional and structural changes in nociceptive receptors and pain transmission neurons at all levels of the neuraxis. This leads to sensitization of peripheral and central nociceptive pathways which initiate and maintain chronic neuropathic pain states.[4] At the level of the dorsal horn, sensitization is primarily mediated by N-Methyl-D-Aspartate (NMDA)-receptor activation.[1] The role of NMDA-receptors in the generation and maintenance of neuropathic pain and CRPS is suggested by clinical and experimental studies and is supported by the benefit of NMDA-receptor antagonists in the treatment of some neuropathic pain.[5]

Clinical studies support the efficacy of ketamine in the treatment of CRPS.[6–9] The analgesic effects of ketamine and its duration of action are dose-dependent. Anesthetic doses of ketamine have not been investigated in pain medicine because of concern for ketamine specific side effects which are also dose-dependent.[5,6] This case report details successful treatment of refractory CRPS with ketamine and midazolam utilized in anesthetic doses that has lasted for 8 years.

## CASE REPORT

A 17-year-old girl suffered a strain injury of the right wrist and hand, which caused severe pain and edema. Initial therapy consisted of immobilization, cooling, and oral diclofenac ($3 \times 50$ mg/day). The patient was re-evaluated after 10 days of treatment because of increasing pain. Further physical therapy and nonsteroidal drugs were continued after this re-evaluation. Severe pain persisted and a low potency opioid (Valoron N®, Pfizer Pharma GmbH, Karlsruhe, Germany: tilidine hydrochloride 50 mg, naloxone hydrochloride 4 mg) was added to her treatment regime, which also failed to provide pain relief.

After 6 months, the patient was transferred to the pain center in Saarbrücken Germany because of continued severe pain, erythema, and edema. She presented with massive edema of the right hand, intense spontaneous superficial and deep pain (mean pain: visual analog scale [VAS] 4, peak pain: VAS 6, on a 10 cm VAS, endpoints: 0: no pain, 10: worst imaginable pain), as well as static and dynamic allodynia of the entire right hand and wrist. The extremity also demonstrated bluish discolored cool skin (temperature difference: 0.5°C), hyperhidrosis in the right forearm, and increased nail and hair growth (Figures 1, 2, 3). A movement disorder was noted that included the inability to initiate movement, make a fist, or oppose the thumb and index finger. The patient fulfillled both the 1993 IASP diagnostic criteria for CRPS, and the 1999 modified research diagnostic criteria for CRPS.[7,8]

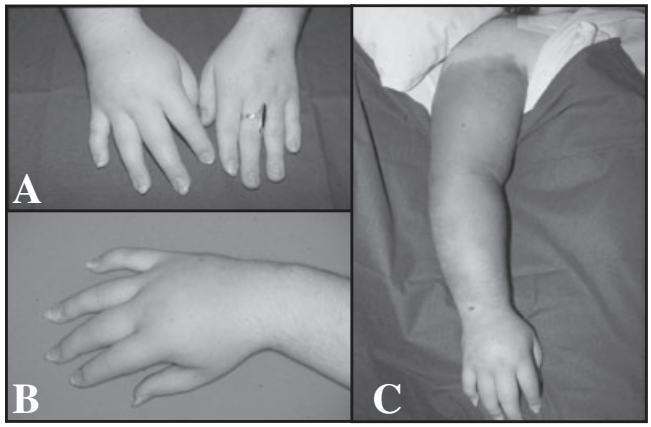


**Figure 1.** Photographs A and B show the clinical signs of the patient at admission to the pain center Saarbrücken. Swelling, reddish discoloration, temperature asymmetry, hyperhidrosis, asymmetric nail, and hair growth were observed. Hyperalgesia and allodynia of the right hand and wrist were severe. Photograph C: status of the patient at admission to the intensive care unit, after the rapid contiguous spread of signs (massive edema, bluish mottled discoloration) into the entire right arm.

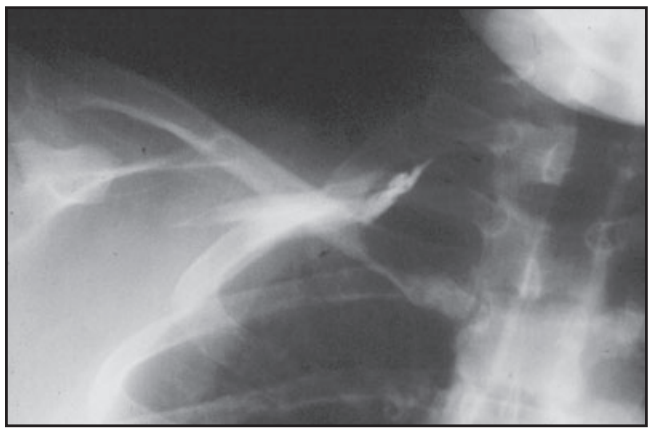

**Figure 2.** Fluoroscopic control of positioning of the brachial plexus catheter (vertical infraclavicular approach), after the loss of the analgesia 24 hours after its insertion and initial pain relief. The contrast demonstrates correct placement of the catheter with diffusion the infra- and supraclavicular components of the brachial plexus.

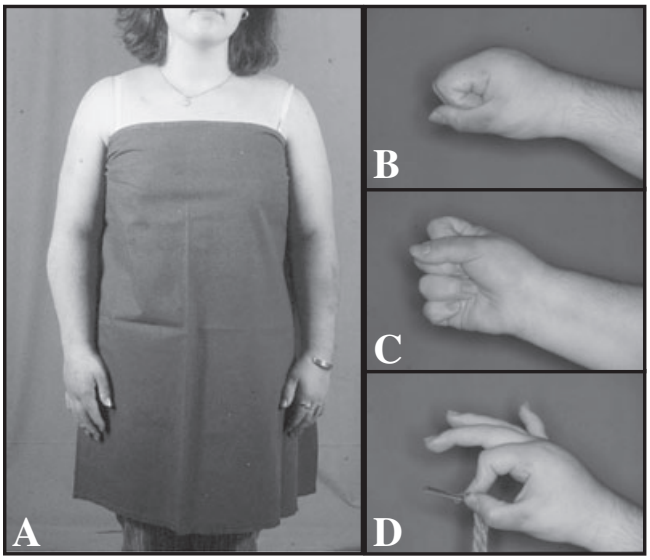


**Figure 3.** Status of the patient following anesthetic treatment with anesthetic doses of ketamine. Photograph A shows the patient 1 week following treatment (resolution of edema and erythema). Photographs B, C, and D show the functional status of the patient 3 months following treatment. B: tight fist closure, lateral aspect, C: tight fist closure (palmar aspect), and D: intact pincer grasp.

Pain reduction (VAS 2) was obtained by continuous brachial plexus analgesia (initial block: 20 mL mepivacaine 1% and 20 mL bupivacaine 0.375%; and then by continuous infusion: of bupivacaine 0.25%, 8 mL/h) in conjunction with physiotherapy. The following day severe pain (VAS 6) recurred. A suspected catheter dislocation was ruled out by fluoroscopy. Subsequent attempts to relieve pain included stellate ganglion blocks, local superior ganglion opioid analgesia, and intravenous opioids, all of which were unsuccessful. Severe edema and discolored skin as well as hyperalgesia and static and dynamic mechanical allodynia were rapidly spreading to her entire arm. She continued to suffer excruciating and unbearable pain (VAS 9 to 9.5). A thrombosis was ruled out by Color-Doppler-Sonography, which was confirmed by a negative magnetic resonance angiogram.

The patient was transferred to the intensive care unit (ICU) for ketamine treatment. Under standard ICU monitoring conditions (continuous arterial blood pressure, ECG, and pulse oximetry), treatment was started with bolus injections of ketamine (1 mg/kg) and midazolam (5 mg), which was then followed by continuous infusions. The ketamine infusion was gradually increased over the following days (3–5 mg/h), and a midazolam infusion was dosed as clinically needed to provide stable and deep sedation. There was rapid regression of the edema and discolored skin, and the patient started to move her hand and arm spontaneously. This regimen was continued for 5 days, at which time edema had completely resolved and spontaneous movements appeared almost unimpaired. On day 6, the infusion was slowly tapered. The patient emerged from anesthetic doses of ketamine and midazolam completely free of pain. She experienced psychomimetic side effects during the first week following treatment that included agitation, anxiety, and nightmares. The psychomimetic side effects responded well to midazolam and completely abated within 1 month.

The patient has remained pain-free and showed a complete remission from associated CRPS signs and symptoms. Her motor function steadily improved with physiotherapy. The patient has maintained this full remission for 8 years.

## DISCUSSION

The exact pathophysiology that underlies CRPS and its optimal treatment is evolving.[1] New insights into the pathophysiology of nociception suggest that sustained painful stimulation leads to activity-dependent neuronal plasticity in peripheral and central nociceptive pathways.[4,9] The resulting central sensitization is believed to be important for the initiation and maintenance of chronic neuropathic pain states as well as CRPS.[1,3] At the spinal level, dorsal horn central pain projecting neurons are posited to be pathologically activated by NMDA-receptor mediated processes, which leads to hyperexcitability and central sensitization.[10] In animal studies, NMDA-receptor antagonists attenuate central sensitization and the establishment of neuropathic pain.[11] Clinical evidence supports the effectiveness of ketamine in the treatment of both neuropathic pain and CRPS.[5,12–15]

Subanesthetic infusion of ketamine was successful in a single case of long-standing CRPS and in a subsequent retrospective larger series of patients.[12,13] In the latter, subanesthetic ketamine was effective in early CRPS when signs and symptoms were localized to distal parts of the affected extremity.[12] In contrast, subanesthetic isomeric ketamine failed to provide relief from pain in refractory and spreading CRPS.[16]

There are several possible mechanisms in addition to or in conjunction with ketamine that may be responsible for the excellent results demonstrated in this patient. The primary analgesic effect of ketamine is thought to be through inhibition of NMDA-receptors. However, ketamine is known to inhibit a variety of other receptors

with an established role in nociception. These include AMPA-, kainate-, and peripheral glutamate receptors as well as different subtypes of opioid and $GABA_A$-receptors, voltage-dependent ion channels (sodium and L-type calcium channels), as well as nicotinergic and muscarinergic acetylcholine receptors.[17–19] Ketamine also is known to inhibit nitric oxide synthase, and to possess anti-inflammatory effects that inhibit proinflammatory cytokines.[6] Thus, ketamine affects various different receptors and mechanisms with established roles in pathological pain. Midazolam, a short-acting benzodiazepine and $GABA_A$-agonist, may also possess analgesic properties.[4,20] Although, it is widely accepted that GABA-ergic mechanisms play a considerable role in central sensitization, almost no evidence exists to support a clinical role for midazolam in the treatment of chronic pain. In the course of central sensitization, GABA-ergic inhibitory transmission is apparently depressed by NMDA-dependent mechanisms that lead to depression of inhibitory transmission and thus potentiates central pain projecting neuron hyperexcitability by disinhibition.[4,20] Enhancement of GABA-ergic inhibitory activity by this $GABA_A$-agonist may have occurred and enhanced ketamine effects. A placebo effect as well as the consequences of 5 days of anesthesia, the latter perhaps "rebooting" pain mechanisms may also play an important role in the procedure.

In conclusion, this report suggests the efficacy of anesthetic ketamine in severe, advanced, and spreading CRPS that is refractory to standard therapy. Because of the intensive care component of this treatment and its associated risks, systematic studies are needed to confirm the impressive effect of this single case, in larger and ideally randomized controlled studies.

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