PAIN MEDICINE CASE REPORTS

Received: 2019-10-03
Accepted: 2020-04-09
Published: 2020-09-30

ISSN 2575-9841

Volume 4, Number 5, pp. 157-162

IV Ketamine-Induced Skin Temperature Changes in a Patient with Unilateral Complex Regional Pain Syndrome (CRPS) Type II

Ashraf F. Hanna, MD[1]
Adam J. Smith, PhD[2]

Background: Ketamine is increasingly being utilized off-label for numerous difficult-to-treat conditions when conservative treatment options fail to provide an adequate clinical response. One such condition is complex regional pain syndrome (CRPS). CRPS is characterized by pain, inflammation, vascular abnormalities, and functional decline. While ketamine has been used successfully to treat the disease, its mechanism of action remains hotly debated and not well-understood.

Case Report: Here, we describe a clinical case of CRPS in a female patient who was refractory to conventional treatment options. Skin temperatures were measured in the affected and unaffected limb before, during, and after intravenous infusion with ketamine. We report that skin temperature increased in the CRPS-affected limb despite the known sympathomimetic effects of ketamine expected to produce vasoconstriction.

Conclusion: The novel findings presented herein are intended to spur formal well-controlled and powered clinical studies, which may better elucidate the vascular effects of ketamine in this underserved patient population.

Key words: Complex regional pain syndrome, depression, esketamine, ketamine hydrochloride, suicidality, thermal imaging

BACKGROUND

Complex regional pain syndrome (CRPS) is a disease state that causes significant pain and limits function of the involved body limb or region. CRPS is commonly attributed to soft tissue damage, bone fractures, or surgery that result in nerve damage (1). However, some cases are not attributed to an identifiable etiology (2). There are 2 types of CRPS: type I occurs with no identifiable cause and type II arises after an injury or trauma to a peripheral nerve (3). The mechanism by which CRPS develops remains unclear but the main characteristics of the disease are continuous pain, sensory disturbances, marked changes in tissue blood flow and skin surface temperature, edema, sweating, movement disorders, and trophic changes of the skin (4). There is evidence that CRPS results from injury to the Aδ- and C- fibers in the peripheral tissues (5). However, the pathophysiology of CRPS appears to be more complex than peripheral nerve damage alone.

Centralization of pain is a theory that repetitive peripheral stimulation causes changes in the central nervous system that, in turn, lead to heightened excitability to noxious stimuli and/or generate the perception of pain in the absence of peripheral input (6). Centraliza-

From: [1]Florida Spine Institute, Clearwater, FL; [2]KemPharm, Inc., Celebration, FL

Corresponding Author: Ashraf F. Hanna, MD, E-mail: ahanna@fsispine.com
Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

tion of pain is often used to describe the spread of pain symptoms in patients with CRPS. Many patients with CRPS experience a spread of pain away from the locus of injury or initial site of symptoms to involve more regions of the body, sometimes even on the contralateral side. This unusual spread of symptoms suggests central nervous system (CNS) involvement in CRPS.

There is a growing body of evidence that implicates vascular abnormalities in CRPS. In the acute phase, the affected limb has been reported to be warmer than the contralateral limb due to cutaneous vasodilation, and a functional inhibition of sympathetic vasoconstrictor activity has been demonstrated (7). This is thought to be caused by an exaggerated inflammatory response, which increases proinflammatory cytokines, leading to vasodilation and an increase in skin temperature (8). After this acute phase, a large number of patients have shown a permanent decrease in blood flow and skin temperature, regarded as the chronic "cold" phase; the CRPS-affected limb is cyanosed and clammy as a result of vasoconstriction and sweating, which suggests that excessive sympathetic nervous system outflow is a driving factor in the progression of CRPS and subsequent pain (8). This line of thought has led many clinicians to use sympathetic blocks for treating late-stage CRPS, which have proven successful in some patients (9).

Ketamine is a long-known N-methyl-D-aspartate (NMDA) receptor antagonist that is conventionally used as an anesthetic agent. More recently, it has been used off-label for a broad spectrum of indications across critical care, emergency medicine, pain medicine, and psychiatry. This explosion in off-label use is the result of significant unmet needs for pharmacotherapeutic options in a myriad of difficult-to-treat indications such as neuropathic pain, treatment-resistant depression, and suicidality to name a few. There is significant evidence supporting the use of ketamine for treating CRPS, including a double-blind placebo-controlled study which found that outpatient intravenous ketamine significantly reduced pain parameters in patients with the disease (10).

Unlike other general anesthetics, ketamine stimulates the cardiovascular system, increasing cardiac output, pulse rate, and arterial and central venous blood pressures (11). These effects have caused many to regard it as a sympathomimetic agent that produces vasoconstriction. The effects of ketamine anesthesia on cardiovascular parameters and catecholamine plasma concentrations were studied in 12 patients with normal cardiovascular function (12). These investigators reported statistically significant rises in heart rate and blood pressure that coincided with rises in plasma adrenaline and noradrenaline concentrations, further supporting the characterization of ketamine as a sympathomimetic agent. In another study, Han et al (13) showed that ketamine inhibits the Ca2+-activated K+ (KCa) channel activity in rabbit cerebral arterial smooth muscle cells causing vasoconstriction. Moreover, ketamine racemate was shown to inhibit levcromakalim-induced vasorelaxation in excised rat aorta tissue in a concentration-dependent manner (14). However, other in vitro studies using rat and rabbit-derived tissues suggest that ketamine produces vasodilation under the conditions tested (15,16). Therefore, the direct vascular effects of ketamine remain debatable.

In the context of the chronic "cold" phase of CRPS that is thought to result from excessive sympathetic nervous system outflow (8), increasing sympathetic tone with ketamine could be counterproductive despite our clinical experience using ketamine in patients with chronic CRPS and the abundance of clinical data showing that ketamine reduces pain levels in patients with chronic CRPS (10,17,18). In the case report described herein, we describe the skin temperature changes of a patient with chronic CRPS, type II of the left lower leg and foot who underwent intravenous ketamine infusion therapy.

CASE REPORT

A 16-year-old female patient with chronic CRPS, type II presented to the Florida Spine Institute (Clearwater, FL) for treatment with intravenous ketamine. This patient had a long history of CRPS related to an ankle injury while playing basketball approximately 5 years ago. Within a month of her injury, her pain escalated to the point where she could no longer walk without assistance from crutches or by using a wheelchair. She was previously diagnosed with CRPS and failed multiple conventional treatment modalities at Boston Children's Hospital. The CRPS affected her left lower leg and foot. She was then transferred to a different clinic and presented with the option of intravenous ketamine for treating her CRPS. She responded well to ketamine and her pain levels had been adequately managed with periodic intravenous ketamine infusions. The patient reported that her pain relief typically lasted for more than 2 months following treatment with ketamine. When her pain returned, maintenance infusions provided significant relief and allowed her to continue with daily activities.

A signed consent form was obtained from the patient's parent. Upon arrival at our clinic, the patient was using a wheelchair due to CRPS-related pain in her left lower leg and foot. She also reported that she was experiencing numbness, tingling, and cold sensations in her affected foot. Prior to starting the ketamine infusion, the patient removed her shoes and socks and acclimated to room temperature (controlled at 75°F throughout the infusion). A FLIR C2 (Lepton 1101 9Hz) (FLIR Systems, Inc., Wilsonville, OR) thermal imaging camera was then used to measure the skin temperature of her left (affected) and right (unaffected) feet prior to starting the infusion. This thermal imaging system claims an accuracy of ± 2% and an operating temperature range of 14°F to 122°F in the product manual. The patient was infused for 4 hours with one mg/kg/h of ketamine. In the middle of the infusion session (t = 2 h), her skin temperatures were measured again. Following the infusion (t = 4.5 h), the skin temperatures of her left and right feet were measured using the thermal imaging camera a final time.

The thermal images are shown in Fig. 1. Minimum, maximum, and mean temperatures were calculated using FLIR Tools Version 5.13.18031.2002 (FLIR Systems, Inc., Wilsonville, OR) and are shown in Table 1. For the patient's left (affected) foot, the mean temperatures pre-, mid-, and postinfusion were 81.4°F, 83.8°F, and 97.3°F, respectively. In her right (unaffected) foot, the mean temperatures pre-, mid-, and post infusion were 82.8°F, 80.6°F, and 91.2°F, respectively.

The patient returned to the clinic for 3 consecutive days for the same infusion treatment. Thermal images were not taken on these subsequent days. Following her final infusion, the patient reported that her pain levels were dramatically lower and that the cold sensation that she had in her left foot had decreased.

DISCUSSION

In this case report, we described the skin temperature changes in a patient with CRPS before, during, and after a ketamine infusion for the first time. Given the known sympathomimetic effects of ketamine, one might expect that the skin temperature would drop during the infusion due to vasoconstriction. In this patient, the skin temperature of the right foot (unaffected) did exhibit a minimal drop during the infusion by 2.2°F. Interestingly, the left foot (affected) increased in temperature during the infusion by 2.4°F. This difference was small, but it is

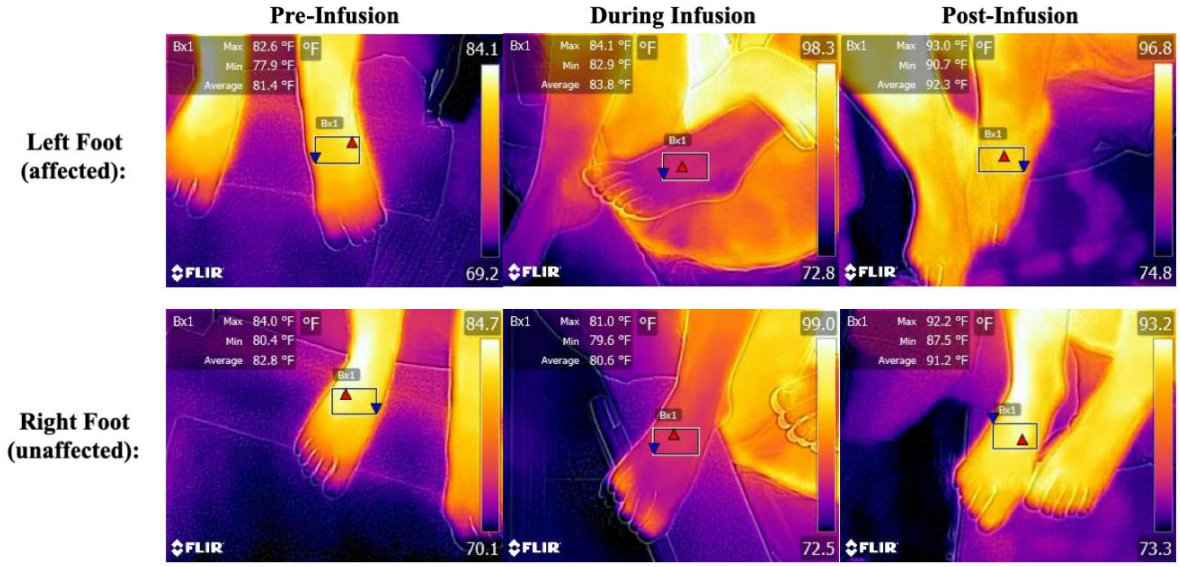

Fig. 1. Thermal images of the CRPS-affected and unaffected foot before, during, and after intravenous infusion with ketamine for 4 hours. The images taken during and post infusion occurred at approximately 2 and 4.5 hours, respectively, from the start of the infusion.

Table 1. Minimum, maximum, and mean temperatures pre-, mid-, and postinfusion of each foot.

		Preinfusion	During Infusion (T = 2 h)	Post Infusion (T = 4.5 h)
Left Foot (affected)	Max Temp (F)	82.6	84.1	93.0
	Min Temp (F)	77.9	82.9	90.7
	Mean Temp (F)	81.4	83.8	97.3
Right Foot (unaffected)	Max Temp (F)	84.0	81.0	92.2
	Min Temp (F)	80.4	79.6	87.5
	Mean Temp (F)	82.8	80.6	91.2

possible that ketamine may interact differently in CRPS-affected limbs compared to normal limbs.

Our working hypothesis is that the sympathomimetic effects of ketamine in the CRPS-affected foot were countered by other effects, which resulted in the skin temperature increase observed in the affected foot. While ketamine is most known as a potent NMDA receptor antagonist, there are numerous other effects that are known. Clinical data have demonstrated that ketamine reduces IL-6 and TNFα in patients undergoing elective abdominal surgery compared to placebo controls (19). These immunomodulatory effects could be a downstream consequence of NMDA-inhibition, but other preclinical data suggests the potential involvement of Toll-like receptor 4 in the anti-inflammatory actions of ketamine (20). A postmortem histopathological study of a patient with chronic CRPS demonstrated increased glial activation and neuronal loss in the posterior horn of the spinal cord compared to control individuals (21). A separate study showed that ketamine inhibited hyperactivation of cultured microglia through the blockade of large conductance Ca2+- and voltage-activated K+ (BK) channels (22). Since CRPS is characterized by inflammation, these anti-inflammatory activities of ketamine are expected to be beneficial and may be involved in the temperature changes that are described in this case report.

In this patient, there was very little difference in the preinfusion skin temperature of the affected and unaffected foot (81.4°F and 82.8°F, respectively). This is in agreement with previous data from Baron et al (23), which showed that skin temperatures of affected and unaffected regions in 6 patients with late-stage CRPS were not different following acclimatization in a warm environment (similar to our test conditions in Florida). The total change in skin temperature from baseline (postinfusion minus preinfusion) for the affected and unaffected foot were 15.9°F and 8.4°F, respectively. This suggests that ketamine may produce an unexpected and exaggerated vasodilatory response in CRPS-affected limbs. However, this assumes that the skin temperature increases observed in the affected limb were due to vasodilation, as this was not directly measured in this patient.

Although the data presented in this case report are interesting, more thorough research under better-controlled conditions should be conducted to properly validate these findings. This case report has a number of limitations that should be considered when interpreting the data. First, this was an observational case study including only a single patient. The patient also changed position during the infusion (Fig. 1). However, a previous study that measured foot temperatures in 39 healthy adults showed that foot temperatures were not correlated with foot activity (24), so this is unlikely to have any impact on the data presented in this case report. Still, these limitations should be considered to avoid overinterpretation of the data presented. This case report is intended to advise potential future studies into the vascular effects of ketamine in patients with CRPS.

REFERENCES

1. Schwartzman RJ, Erwin KL, Alexander GM. The natural history of complex regional pain syndrome. ***Clin J Pain*** 2009; 25:273-280.
2. Stanton-Hicks MD, Burton AW, Bruehl SP, et al. An updated interdisciplinary clinical pathway for CRPS: Report of an expert panel. ***Pain Pract*** 2002; 2:1-16.
3. Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: Changing concepts and taxonomy. ***Pain*** 1995; 63:127-133.
4. Groeneweg G, Huygen FJ, Niehof SP, et al. Effect of tadalafil on blood flow, pain, and function in chronic cold complex regional pain syndrome: A randomized controlled trial. ***BMC Musculoskelet Disord*** 2008; 9:143.
5. Wasner G, Schattschneider J, Binder A, Baron R. Complex regional pain syndrome--diagnostic, mechanisms, CNS involvement and therapy. ***Spinal Cord*** 2003; 41:61-75.
6. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. ***Pain*** 2011; 152(3 Suppl): S2-S15.
7. Groeneweg G, Huygen FJ, Coderre TJ, Zijlstra FJ. Regulation of peripheral blood flow in complex regional pain syndrome: Clinical implication for symptomatic relief and pain management. ***BMC Musculoskelet Disord*** 2009; 10:116.
8. Goh EL, Chidambaram S, Ma D. Complex regional pain syndrome: A recent update. ***Burns Trauma*** 2017; 5:2.
9. Gungor S, Aiyer R, Baykoca B. Sympathetic blocks for the treatment of complex regional pain syndrome: A case series. ***Medicine (Baltimore)*** 2018; 97:e0705.
10. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: A double-blind placebo controlled study. ***Pain*** 2009; 147:107-115.
11. Folts JD, Afonso S, Rowe GG. Systemic and coronary haemodynamic effects of ketamine in intact anaesthetized and unanaesthetized dogs. ***Br J Anaesth*** 1975; 47:686-694.
12. Appel E, Dudziak R, Palm D, Wnuk A. Sympathoneuronal and sympathoadrenal activation during ketamine anesthesia. ***Eur J Clin Pharmacol*** 1979; 16:91-95.
13. Han J, Kim N, Joo H, Kim E. Ketamine blocks Ca2+-activated K+ channels in rabbit cerebral arterial smooth muscle cells. ***Am J Physiol Heart Circ Physiol*** 2003; 285:H1347-H1355.
14. Dojo M, Kinoshita H, Iranami H, Nakahata K, Kimoto Y, Hatano Y. Ketamine stereoselectively affects vasorelaxation mediated by ATP-sensitive K(+) channels in the rat aorta. ***Anesthesiology*** 2002; 97:882-886.
15. Noh HJ, Bae YM, Park SH, et al. The vasodilatory effect of ketamine is independent of the N-methyl-D-aspartate receptor: Lack of functional N-methyl-D-aspartate receptors in rat mesenteric artery smooth muscle. ***Eur J Anaesthesiol*** 2009; 26:676-682.
16. Yamazaki M, Momose Y, Shakunaga K, Kamitani K, Ito Y. The vasodilatory effects of ketamine on isolated rabbit portal veins. ***Pharmacol Toxicol*** 1995; 76:3-8.
17. Kiefer RT, Rohr P, Ploppa A, Altemeyer KH, Schwartzman RJ. Complete recovery from intractable complex regional pain syndrome, CRPS-type I, following anesthetic ketamine and midazolam. ***Pain Pract*** 2007; 7:147-150.
18. Nama S, Meenan DR, Fritz WT. The use of sub-anesthetic intravenous ketamine and adjuvant dexmedetomidine when treating acute pain from CRPS. ***Pain Physician*** 2010; 13:365-368.
19. Beilin B, Rusabrov Y, Shapira Y, et al. Low-dose ketamine affects immune responses in humans during the early postoperative period. ***Br J Anaesth*** 2007; 99:522-527.
20. Yu M, Shao D, Feng X, Duan M, Xu J. Effects of ketamine on pulmonary TLR4 expression and NF-kappa-B activation during endotoxemia in rats. ***Methods Find Exp Clin Pharmacol*** 2007; 29:395-399.
21. Del Valle L, Schwartzman RJ, Alexander G. Spinal cord histopathological alterations in a patient with longstanding complex regional pain syndrome. ***Brain Behav Immun*** 2009; 23:85-91.
22. Hayashi Y, Kawaji K, Sun L, et al. Microglial Ca(2+)-activated K(+) channels are possible molecular targets for the analgesic effects of S-ketamine on neuropathic pain. ***J Neurosci*** 2011; 31:17370-17382.
23. Baron R, Maier C. Reflex sympathetic dystrophy: Skin blood flow, sympathetic vasoconstrictor reflexes and pain before and after surgical sympathectomy. ***Pain*** 1996; 67:317-326.
24. Nardin RA, Fogerson PM, Nie R, Rutkove SB. Foot temperature in healthy individuals: Effects of ambient temperature and age. ***J Am Podiatr Med Assoc*** 2010; 100:258-264.