Title

Intravenous Ketamine Administered as Patient Controlled Analgesia and Continuous Infusion for Central Pain Syndrome

Journal

Journal of Pain & Palliative Care Pharmacotherapy, 35(1)

ISSN

1536-0288

Authors

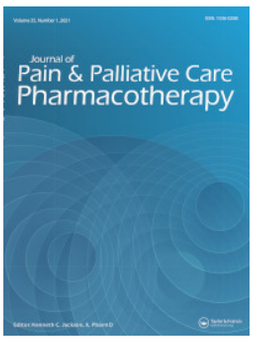
Wang, Alex J
Eid, Tarek
Skavinski, Kira
et al.

Publication Date

2021-01-02

DOI

10.1080/15360288.2020.1814480



Taylor & Francis
Taylor & Francis Group

Journal of Pain & Palliative Care Pharmacotherapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ippc20

Intravenous Ketamine Administered as Patient Controlled Analgesia and Continuous Infusion for Central Pain Syndrome

Alex J. Wang, Tarek Eid, Kira Skavinski, Ajay N. Sharma & Solomon Liao

To cite this article: Alex J. Wang, Tarek Eid, Kira Skavinski, Ajay N. Sharma & Solomon Liao (2021) Intravenous Ketamine Administered as Patient Controlled Analgesia and Continuous Infusion for Central Pain Syndrome, Journal of Pain & Palliative Care Pharmacotherapy, 35:1, 38-42, DOI: 10.1080/15360288.2020.1814480

To link to this article: https://doi.org/10.1080/15360288.2020.1814480

JOURNAL OF PAIN & PALLIATIVE CARE PHARMACOTHERAPY
2021, VOL. 35, NO. 1, 38–42
https://doi.org/10.1080/15360288.2020.1814480

Taylor & Francis
Taylor & Francis Group

CASE REPORT

Intravenous Ketamine Administered as Patient Controlled Analgesia and Continuous Infusion for Central Pain Syndrome

Alex J. Wang, Tarek Eid, Kira Skavinski, Ajay N. Sharma, and Solomon Liao

ABSTRACT

Treatment of Central Pain Syndrome (CPS) is known to be extremely challenging. Current therapies are unsatisfactory as patients report only mild to moderate pain relief. We report a case of using ketamine as a patient-controlled analgesia (PCA) for the treatment of CPS. A 58-year-old male with CPS presented with severe generalized body pain refractory to multiple pharmacological interventions. He was started on a basal infusion rate at 0.3 mg/kg/h with a ketamine PCA bolus of 10 mg with a 10-minute lockout period. Over the next 7 days, the basal infusion rate was titrated up to 2.1 mg/kg/h relative to the number of times the patient pressed the PCA. At the end of the trial, the patient reported 0/10 pain with lightheadedness on the first day being the only side effect reported. He was discharged home with his regular pain regimen, with significant decrease in pain over the next few months. Rather than trying to establish a "one size fits all" protocol for ketamine infusions, this case illustrates a shift in pain management focus by allowing patients to self-titrate and demonstrates the potential for using ketamine PCA as a treatment option for CPS.

ARTICLE HISTORY
Received 6 December 2019
Revised 23 May 2020
Accepted 19 August 2020

KEYWORDS
Ketamine; PCA; pain; refractory; NMDA antagonist

Introduction

Central pain syndrome (CPS) is a neurological condition where the pain-transmission pathways of the central nervous system (CNS) are disrupted, leading to increased pain. Previously, this syndrome was termed thalamic pain syndrome, Dejerine-Roussy syndrome, or central post-stroke syndrome. Disruption anywhere along the pain-transmission pathway, which includes the spinal cord, thalamus, and sensory cortex, alters the CNS's ability to process pain. There are numerous etiologies to CNS damage such as stroke, tumors, multiple sclerosis, and trauma. Due to the variety in etiology and location of the pain-pathway disruption, symptoms can vary widely among patients. Pain may occur in any area of the body and has been described as burning, tingling, pins and needles, or stabbing. It may also be intermittent or constant and may vary widely in severity. Unfortunately, most patients experience a constant, moderate to severe pain which is debilitating and has a significant impact on quality of life. The underlying mechanism behind the pain is unclear. It is proposed that damage to the pain-transmission pathways leads to neuronal hyperexcitability (1,2). CPS is a prevalent disease that affects millions of people worldwide. Approximately 5-10% of stroke patients, 30% of multiple sclerosis patients, and up to 40% of spinal cord injury patients experience CPS.

Treatment of CPS is known to be extremely challenging and ineffective due to the unknown pathophysiology of the disease and the fact that patients present with a myriad of symptoms. Current therapies include tricyclic antidepressants (TCAs), lamotrigine, and gabapentin. These treatments are found to be unsatisfactory as patients report only mild to moderate pain relief and state that complete pain relief is unattainable. Further investigations are needed to establish more efficacious treatments for CPS. Ketamine has been described in one prior case report as being successful in the treatment of Ehlers-Danlos induced CPS (3).

Alex J. Wang, Tarek Eid, Kira Skavinski, Ajay N. Sharma, and Solomon Liao are with the School of Medicine, University of California, Irvine, Irvine, California, USA; Department of Internal Medicine, University of California, Irvine, Irvine, California, USA; Department of Internal Medicine, University of California, San Diego, San Diego, California, USA.
CONTACT Solomon Liao, MD FAAHPM ssliao@uci.edu Clinical Professor of Medicine, Director of Palliative Care Service, Department of Internal Medicine, UC Irvine Medical Center, University of California, Irvine, Building 26, Suite 1001, Irvine, CA 714-456-5003, USA.

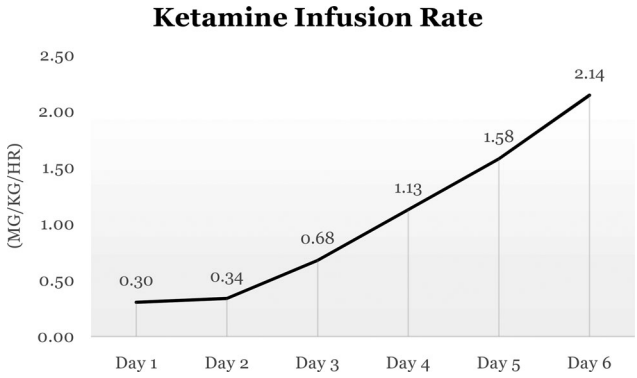


Figure 1. Ketamine infusion rate over hospital course.

Ketamine was first approved as a general anesthetic by the United States Food and Drug Administration (FDA) in 1970 and is widely used today both as an anesthetic, analgesic, and antidepressant. It has been studied as a possible treatment for conditions such as complex regional pain syndrome (CPRS), chronic pain, depression, post-traumatic stress disorder, and other neuropathic pain syndromes (4). Although the exact mechanism of action of ketamine is unknown due to its wide variety of molecular effects, studies have shown that ketamine primarily functions as a N-methyl-D-aspartate (NMDA) receptor antagonist (5). It prevents the release of glutamate, the predominant excitatory neurotransmitter in the central nervous system (CNS), and plays an inhibitory role on the pain signal propagation pathway. More recently, ketamine has also been shown to inhibit substance P receptors, causing a greater reduction in pain especially during painful hyperalgesic states (6).

This paper reports an illustrative case of a patient using ketamine as a patient-controlled analgesia (PCA) for the treatment of CPS secondary to corticobasal degeneration.

Case description

A 58-year-old Caucasian male was referred to our palliative care clinic for management of "complex regional pain syndrome" (CRPS) secondary to corticobasal degeneration. His past medical history was significant for anxiety and depression. He first developed pain in his right wrist following a fall 3 years prior, which subsequently spread to his right arm, shoulder, back, and right leg 4 months later. Thus, his diagnosis was switched to CPS rather than CRPS. The pain was characterized as a burning sensation across his shoulder and back with allodynia and hypesthesia at his right heel. Pain severity was rated at maximum 8 out of 10 and at minimum 5 out of 10, which interfered with his sleep every night. He had lost most of the function in his right arm and was confined to a wheelchair due to weakness in his right leg. He also had impaired speech, a chronic cough, and dysphagia, which made it difficult for him to consume foods. Exam was notable for dysarthria, masked facies, right ear hearing loss, bilateral cogwheel rigidity that is worse on the right, significant right-hand apraxia, hypersensitivity of right hand, forearm, and right leg, and 3 out 5 strength in the right lower extremity. For pain control, he was on hydrocodone 10 mg/acetaminophen 325 mg every 4 hours as needed, tramadol 50 mg every 8 hours as needed, gabapentin 600 mg in the morning, 600 mg in the afternoon, and 1200 mg at night, tizanidine 4 mg daily, venlafaxine 37.5 mg twice a day, and topical lidocaine cream 3 times a day as needed. He trialed a low dosage ketamine infusion regimen at an outside hospital which did not help his pain and instead led to hallucinations. Despite all these medications, he continued to experience debilitating pain.

One week after his initial clinic visit, he was admitted to the hospital for initiation of ketamine infusion utilizing a patient-controlled analgesia (PCA) pump. All home pain medications except for venlafaxine were held throughout admission. Upon arrival to the hospital and shortly prior to the initiation of the ketamine infusion, quetiapine 25 mg every 6 hours oral was initiated for hallucination prophylaxis. On the first day, he was started on a ketamine basal infusion of 0.3 mg/kg/h and reported a decrease in pain severity to 4 out of 10 within minutes. The following day the ketamine basal dosage was increased to 0.33 mg/kg/h, and the patient was started on a ketamine PCA bolus of 10 mg every 10 minutes as needed. In the following days, the ketamine infusion rate was increased to match the total dose of ketamine received; basal rate plus boluses, divided by 24 hours, as would be done with an opioid PCA. The final infusion rate reached was 2.1 mg/kg/h (Figure 1). Lightheadedness on the first day was

the only reported side effect. The patient never reported hallucinations, nightmares, or dream-like sensations during his ketamine course. His pain level continually decreased until day 6 when he reported a pain severity of 0.

After 7 days of ketamine infusion, the patient was discharged home with prescriptions for gabapentin 600 mg twice a day, oxycodone 10 mg/acetaminophen 325 mg every 6 hours as needed, tramadol 50 mg twice a day as needed, tizanidine 4 mg daily as needed, and venlafaxine 75 mg twice a day to manage his pain. On his clinic follow-up visit 1 week after discharge, the patient reported significant pain relief which allowed him to sleep throughout the night. One month later, the patient returned to clinic with significant improvement in his pain level and daily activities of living. His pain, which he rated a 2 out of 10, was adequately controlled, he began walking again, and was able to speak without difficulty. His dysphagia and chronic cough dissipated to the point where he could tolerate a regular diet. In addition, he stated that he was sleeping 8 hours a night.

Discussion

This case illustrates the successful use of a ketamine PCA for the treatment of Central Pain Syndrome secondary to Corticobasal Degeneration. Corticobasal Degeneration is a rare progressive neurological disorder which leads to neuronal loss in the brain. The patient was initially diagnosed with Complex Regional Pain Syndrome before being diagnosed with Central Pain Syndrome at our clinic. His presenting symptom of burning pain along the entire right side of his body was more consistent with CPS than with CRPS, which usually presents in a single limb after an injury. As with most patients with CPS, our patient trialed several pain regimens but failed to find adequate pain relief. He remained confined to a wheelchair, experienced insomnia, dysphagia, and was in constant pain, leading to depression. Treatment with ketamine PCA proved to be a life-altering therapy for this patient.

As has been reported in the literature, the analgesic effect of ketamine can last for a significantly long time even after the drug or its metabolite, norketamine, has been excreted from the body (5). The duration of this effect is variable between individuals but can last up to a few weeks (5). The mechanism of this lingering effect is unknown but suggests that ketamine somehow "resets" the central nervous system's response to pain. One possible explanation for the long-lasting analgesic effects of ketamine is that it modulates gene expression pathways that control the development of chronic pain. Studies have shown that ketamine regulates NMDA receptor expression, astrocytic activation, and synaptic structure (5). Any physical structural remodeling of the brain could lead to long-lasting effects of pain alleviation past the detectable presence of ketamine or its metabolites.

Randomized controlled trials have shown that prolonged ketamine infusion leads to longer lasting analgesic effect when compared to shorter duration infusions. In one randomized double-blind placebo-controlled study, Complex Regional Pain Syndrome Type 1 patients experienced analgesia for up to 3 months.[7] These findings were replicated in another study where CRPS patients were treated with 10 days of daily 4-hour ketamine infusions (7). On the other hand, a study performed on fibromyalgia patients revealed that a 30-minute infusion of ketamine provided analgesia for about 45 minutes (3).

Despite the increase in clinical use, there is a wide range of intravenous (IV) ketamine infusion protocols among the literature (6,8). A recent review article by Cohen et al. from the American Society of Regional Anesthesia and Pain Medicine attempted to establish a consensus guideline on the use of IV ketamine infusion (6). However, after analyzing and reviewing multiple reports, they were unable to provide an established protocol for the use of IV ketamine. They reported that there were too many confounding variables and poor translational reproducibility based on differing patient characteristics (5). Multiple studies in the literature have reported different ketamine infusion protocols with varying durations of infusion, total infusion doses, infusion rates, and combination drug protocols, but none have agreed on established guidelines (5,6).

Rather than trying to establish a "one size fits all" protocol for IV ketamine infusions, this case illustrates a shift in focus by allowing the patient to self-titrate. This concept is similar to PCA titration already in use with opioids, which allows patients to self-administer small doses of the medication, rather than trying to guess their pain medication requirement (9). PCAs tailor the dosage of medication to the individual's pain and give patients the control to stop administering the medication whenever side effects begin. Multiple studies have shown that PCAs have increased safety, better pain management, and result in higher patient satisfaction than non-patient-controlled analgesia (8,10). Ketamine, which has less severe side effects than opioids, can just as easily be administered through a PCA.

Current published literature starts with an initial IV ketamine infusion rate between $0.1 - 0.5$ mg/kg/h (6). Most clinicians choose the rate based on their own clinical experience and side effect profiles of their patients. In this case, we started the patient on an infusion rate of 0.3 mg/kg/h. However, the patient had trialed ketamine before at another hospital, which meant he was cognizant about the potential adverse side effects. Since the patient was able to titrate his own ketamine infusion, he continued to increase the infusion rate until reaching a therapeutic dose by the end of the week. This approach allowed him to reach a higher infusion rate of 2.1 mg/kg/h without experiencing any adverse side effects. At the end of the week, the patient was able to discontinue IV ketamine use as soon as his pain level was controlled and did not report any withdrawal symptoms afterwards.

This case also highlights the effectiveness of ketamine as a treatment for depression in conjunction with chronic pain. Chronic pain and depression are often closely linked, and many antidepressant drugs do not treat pain (11). Ketamine, on the other hand, was recently approved by the FDA as a treatment for major depression and demonstrates a lasting antidepressant efficacy (12). The mechanism behind ketamine's antidepressant effects are unknown but are thought to be related to the inhibition of NMDA receptors, leading to increased production of proteins that are normally decreased in patients with major depression (13). The advantage of ketamine is that it can simultaneously treat a patient's physical pain as well as their emotional pain.

Ketamine infusion is associated with potentially serious side-effects and should only be used in patients with pain refractory to first-line therapies. Side-effects include hallucinations, agitation, anxiety, cardiovascular stimulation, and hepatotoxicity. Premedication can be given in conjunction with ketamine to reduce the risk of developing side-effects. In our patient, a previous trial of low dose ketamine led to development of hallucinations. Therefore, quetiapine was given prophylactically during the 7-day course of ketamine infusion with PCA. Given his history of depression and past experience of hallucinations, we selected quetiapine, an atypical antipsychotic, as a premedication. The starting dose was quetiapine 25 mg every 6 hours with the possibility of up-titrating to 75 mg if his hallucination side effects persisted. However, if the patient did not have a history of depression, we would have administered Midazolam as a premedication since it has been shown to reduce the risk of agitation prior to ketamine administration (14). Premedication prior the administration of ketamine is an effective way to prevent side effects and should be chosen based on patient characteristics.

This unique case demonstrates the effectiveness and safety of titrating ketamine by using a PCA in conjunction with a continuous infusion and suggests that ketamine may be a viable option for patients who have Central Pain Syndrome refractory to traditional therapy, especially if they have coexisting depression. More research is necessary to examine ketamine's use as a PCA and in Central Pain Syndrome.

Disclosure statement

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

ORCID

Alex J. Wang http://orcid.org/0000-0003-3653-9756
Ajay N. Sharma http://orcid.org/0000-0002-0078-4322

References

1. Kuan Y-H, Shyu B-C. Nociceptive transmission and modulation via P2X receptors in central pain syndrome. Mol Brain. 2016;9(1):58. doi:10.1186/s13041-016-0240-4.
2. Canavero S, Bonicalzi V. Extradural cortical stimulation for central pain. Acta Neurochir Suppl. 2007; 97(Pt 2):27–36. doi:10.1007/978-3-211-33081-4_3.
3. Noppers I, Niesters M, Swartjes M, Bauer M, Aarts L, Geleijnse N, Mooren R, Dahanl A, Sarton E. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur J Pain. 2011;15(9):942–9. doi:10.1016/j.ejpain.2011.03.008.
4. Sleigh J, Harvey M, Voss L, Denny B. Ketamine – more mechanisms of action than just NMDA blockade. Trends Anaesth Crit Care. 2014;4(2–3):76–81. doi:10.1016/j.tacc.2014.03.002.
5. Iacobucci GJ, Visnjevac O, Pourafkari L, Nader ND. Ketamine: an update on cellular and subcellular mechanisms with implications for clinical practice. Pain Phys. 2017;20(2):E285–E301. doi:10.36076/ppj.2017.E301.
6. Cohen SP, Bhatia A, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018; 43(5):521–46. doi:10.1097/AAP.0000000000000808.
7. Sigtermans MJ, et al. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. Pain. 2009;145(3): 304–11. doi:10.1016/j.pain.2009.06.023.
8. Geisser ME, Roth RS, Theisen ME, Robinson ME, Riley JL. Negative affect, self-report of depressive symptoms, and clinical depression: relation to the experience of chronic pain. Clin J Pain. 2000;16(2): 110–20. doi:10.1097/00002508-200006000-00004.
9. Assouline B, Tramèr MR, Kreienbühl L, Elia N. Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: systematic review and meta-analyses of randomized controlled trials with trial sequential analyses. Pain. 2016;157(12):2854–64. doi:10.1097/j.pain.0000000000000705.
10. McNicol ED, Ferguson MC, Hudcova J. Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain. Cochrane Database Syst Rev. 2015, Issue 6. Art. No.: CD003348. doi:10.1002/14651858.CD003348.pub3.
11. Romeo B, Choucha W, Fossati P, Rotge J-Y. Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. Psychiatry Res. 2015;230(2):682–8. doi:10.1016/j.psychres.2015.10.032.
12. Strasburger SE, Bhimani PM, Kaabe JH, Krysiak JT, Nanchanatt DL, Nguyen TN, Pough KA, Prince TA, Ramsey NS, Savsani KH, et al. What is the mechanism of Ketamine's rapid-onset antidepressant effect? A concise overview of the surprisingly large number of possibilities . J Clin Pharm Ther. 2017;42(2):147–54. doi:10.1111/jcpt.12497.
13. Lo TCT, Yeung ST, Lee S, Skavinski K, Liao S. Reduction of Central Neuropathic Pain with Ketamine Infusion in a Patient with Ehlers-Danlos syndrome: a case report. J Pain Res. 2016;9:683–7. doi:10.2147/jpr.s110261.
14. Somashekara SC, Govindadas D, Devashankaraiah G, et al. Midazolam premedication in attenuating ketamine psychic sequelae. J Basic Clin Pharm. 2010;1(4): 209–13.