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### **Title**

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### **Permalink**

<https://escholarship.org/uc/item/1hv021nn>

### **Journal**

Proceedings of UCLA Health, 25(1)

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### **Publication Date**

2021-06-03

## CLINICAL VIGNETTE

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# Sickle Cell Pain Crisis Complicated by Opioid Induced Hyperalgesia, Treated with Low Dose Ketamine Infusion

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### Abstract

Hospital admissions of patients with sickle cell disease is mainly due to acute pain from a vaso-occlusive crisis (VOC).<sup>1</sup> Management of VOC is challenging and requires, IV fluid, oxygen and significant doses of intravenous (IV) opioids. However, in a subset of cases this can adversely result in opioid induced hyperalgesia. In the event of opioid induced hyperalgesia, particularly in those being treated for sickle cell crisis,<sup>2</sup> some suggest the use of low dose Ketamine for pain control. We present a case of a 36-year-old female, with VOC, who experienced worsening pain despite increasing doses of IV Hydromorphone, only partially alleviated by scorching hot showers. Tentative diagnosis of opioid induced hyperalgesia was made, and subsequently treated with low dose ketamine infusion which resulted in a dramatic resolution of her pain and symptoms. Ketamine offers a potent therapeutic tool to manage pain acutely and safely rotate to a different class of opioids.

### Introduction

Sickle cell disease can present with acute vaso-occlusive pain. Common locations include back chest, abdomen, and long bones. Neuropathic pain can also have components of central sensitization, peripheral injury, and hyperalgesia. Complications can include abnormal vital signs, leukopenia, leukocytosis, worsening anemia, hepatic or splenic sequestration of blood, pain associated with abdominal distention, jaundice, and hematuria. Depending on the clinical picture, treatment considerations include oxygen therapy, opioid analgesics, blood transfusions, and IV fluids.<sup>1</sup>

Opioid induced hyperalgesia (OIH) can be associated with conditions in which opioids are used as primary pain management such as with sickle cell VOC. Mechanisms include sensitization of primary afferent neurons, and spinal dynorphins that, together, enhance nociceptive input.<sup>2</sup> Ketamine serves as an N-Methyl-D-aspartic acid (NMDA) receptors antagonist, thus directly targeting one of the primary causes of an OIH state.<sup>3</sup>

### Case

A 36-year-old female with lifelong SS genotype sickle cell disease was admitted for a VOC, reminiscent of her previous crises. She reported diffuse pain to arms, legs, and back for four days and was unable to alleviate her pain at home with

prescribed breakthrough oral Hydromorphone 4 mg, Hydrocodone-Acetaminophen 10-325 mg, Gabapentin 800 mg, and Tizanidine 4 mg. Her history is significant for multiple recurrent uncontrolled pain episodes of similar nature as well as use of Crizanlizumab (ADAKVEO) due to frequent hospital admissions for pain control. Unfortunately, despite this regimen she continued to experience chronic and intermittent pain as a result of her sickle cell disease.

On hospital day 3, the patient complained of persistent and exacerbated pain while on IV hydromorphone administration. The frequency of IV hydromorphone was steadily increased from 4 mg IV every 4 hours to every 3 hours and later again increased to 5mg. Unfortunately, there was no improvement in her pain and in fact it appeared to be worsening. Clinical suspicion was that her exacerbated pain was possibly a result of a superimposed infection given her oral temperature of 38C with a positive blood culture for staph hominis in one of two bottles, which was later concluded to a contaminant, even though patient was initially treated with antibiotics with resolution of her fever. Her chest x-ray shows prominent pulmonary vascular congestion, requiring further evaluation with CT chest that show multiple ill-defined nodules throughout both lungs measuring up to 0.8 cm in the left upper lobe. Differential diagnosis including septic emboli was made, transthoracic echocardiogram negative for endocarditis.

On hospital day 4 the patient complained the entire night of severe and increasing body pain, and on hospital day 5 her pain became unbearable to the point that she was crying of severe unrelenting pain. Furthermore, the patient climbed out of her hospital bed and ran to the hallway complaining of severe pain and demanding to go to the emergency room for continuous infusion of IV hydromorphone. She subsequently took off her clothes stating it was "burning her skin" and ran into the bathroom to start a scorching hot shower in an attempt to ease her pain. After which multiple nurses, two attendings, and house staff were able to extract her out of the shower after 15 minutes and was placed on her bed.

Patient then described the event as follows: "I have severe "Sickle Pain " I get IV hydromorphone and the pain goes away in a few minutes, but it only disappears for about 5 minutes and then I get more intense severe pain all over my body worse than

before! My skin burns all over and anything touching me makes it worse and only very hot water eases it.”

A tentative diagnosis of OIH in the setting of concomitant sickle cell pain crisis was made by the team and intervention was immediately made with IV infusion of continuous Ketamine at 0.1 mg/kg/hr, which was increased to 0.2 mg/kg/hr 6 hours later with dramatic resolution of her pain and symptoms. The IV hydromorphone was discontinued and for the next 48 hours she did not require a single dose of hydromorphone but remained on her oral maintenance MS Contin.

After 48 hours the patient stated that “this is the best pain relief she has ever experienced in her life”.

### Discussion

The proposed mechanism for the development of Opioid-induced Hyperalgesia (OIH) involves the central glutaminergic system. When the glutamate transporter system is inhibited, there is an increase in the amount of glutamate available to excitatory N-Methyl-D-aspartic acid (NMDA) receptors. It is proposed that there is cross talk of neural mechanism of pain and tolerance. When morphine is administered, it becomes neurotoxic via the NMDA receptor mediated apoptotic cell death of the dorsal horn. This then sensitizes the neuron and may partially explain the development of OIH. Additionally, spinal dynorphins may also increase the presence of excitatory NMDA receptors.<sup>2</sup>

Ketamine is a very potent inhibitor of NMDA receptors. The proposed therapeutic mechanism is that ketamine reduces the hypersensitive state. After the ketamine drip is discontinued, patients do not revert back to their OIH state, allowing the physician a chance to safely return to longer-acting opioids. Attempting to rotate opioids also helps in preventing the return to an OIH state.

Sickle-Cell patients will often need lifelong pain management medication; therefore, OIH is a possible complication. As the analgesic effect of opioids diminishes, 3 differentials come to mind: Increased opioid tolerance, worsening pain state, and opioid induced hyperalgesia. Each differential has unique mechanisms and therapeutic approaches.

In opioid tolerance, the receptors are desensitized while also having super-activation of the cAMP pathway. To treat, the opioid dose is escalated, longer-acting opioids are started, nonopioid analgesics are added, and drugs that prevent or delay tolerance are added, like Gabapentin.

In a worsening pain state, the disease is progressing, neuropathic pain may be included, and there may be an enhanced opioid metabolism. To treat, opioid dosage is escalated, nonopioid analgesics are added, and treatment is started for neuropathic pain or other pain mechanisms.<sup>4</sup>

In opioid induced hyperalgesia, there is a sensitization of primary afferent neurons, and activation of dynorphin and central glutamatergic systems. In addition to tapering the opioid dosage, NMDA antagonists like Ketamine offer an opportunity to block the OIH mechanism, and allow the restarting of long-acting opioids. It is also advised to rotate opioids to reduce the chances of reverting to an OIH state.

Therapeutic approaches of OIH include tapering opioid doses, trying longer-acting opioids, attempting rotation of opioids as well as adding NMDA agonists such as Ketamine. Ketamine studies recommend IV administration utilizing 4 doses: 0.05 mg/kg/hr, 0.1 mg/kg/hr, 0.15 mg/kg/hr, and 0.2 mg/kg/hr. Patients begin the Ketamine infusion at 0.05 mg/kg/hr. Four or more hours after infusion started, the dose may be increased to 0.1mg/kg/hr if the pain is not improved to an acceptable level and side effects remain acceptable. Four hours or more after the previous increase, the dose may be adjusted to 0.15 mg/kg/hr. Four hours or more after the previous increase, the dose may be adjusted to 0.2 mg/kg/hr. The maximum dose of ketamine is limited to 300 mg per 24hrs.<sup>3</sup>

### Conclusion

As a noncompetitive antagonist of NMDA receptors, Ketamine has been shown to modulate OIH and opioid tolerance. Few publications have reported on use of low-dose ketamine to manage pain during VOC. It could be considered as an adjunct analgesic agent during VOC episodes in patients that report persistent severe pain despite receiving increasing high-dose opioid therapy.<sup>3</sup>

**Informed Consent:** Informed signed consent was obtained from the patient for their anonymized information to be published in this article.

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