
**Ketamine Infusion for Sickle Cell Crisis Pain in an Adult**

To the Editor:

There is no single drug or combination of medications that completely alleviates sickle cell crisis pain. Sickle cell crises may occur in the setting of chronic or recurrent pain, chronic opioid use, and relative opioid tolerance, making crises particularly difficult to treat. A variety of adjunctive analgesics have been tried, including ketamine.\(^1\)\(^2\) By blocking the N-methyl-D-aspartate (NMDA) receptor, ketamine impairs sensitization of spinal neurons to nociceptive stimuli and may, therefore, impede development of and blunt neuropathic pain.\(^3\)

Ketamine was demonstrated to be useful in a small pediatric population with sickle cell crisis pain.\(^2\) Ketamine is used widely in adults with severe pain not related to sickle cell disease. Subramaniam et al. performed a systematic review of 37 randomized, double-blind, clinical trials of ketamine used as an adjunct to opioids in postsurgical patients (both children and adults). They concluded that low-dose ketamine is helpful and safe when added to opioid analgesia in postoperative patients.\(^4\)

In a second meta-analysis, Bell et al. reported a similar role for ketamine in a postsurgical population.\(^5\) Ketamine has been shown, anecdotally, to help manage a variety of adult opioid-refractory nonsurgical pains as well.\(^6\)

Given this experience, we hypothesized that ketamine might be useful in the management of adult sickle cell crises. Few or no reports exist, however, describing this particular use of the drug. We describe the case of a 31-year-old man in sickle cell crisis treated with ketamine as an adjunct to opioids.

**Case**

A 31-year-old man presented to the emergency department in vaso-occlusive pain crisis after two weeks of worsening hip, shoulder, and knee pain refractory to oral opioids. The patient endorsed general good health excepting sickle cell disease and related chronic pain, hypertension, and gall bladder disease. A review of systems was positive only for cough and mild dyspnea on exertion. Pertinent findings on physical examination included icterus of the sclera and mucous membranes. The patient’s at-home medications were extended-release oxycodone 40 mg twice daily and oxycodone/acetaminophen (10/325) tablets as needed. Hydroxyurea had been discontinued by the patient’s hematologist a month before admission. The patient was given intravenous (IV) hydromorphone and IV fluids in the emergency department before being admitted.

Per the patient’s report, previous pain crises lasted approximately two weeks and were difficult to treat. The patient had, in fact, ended two previous admissions against medical advice, citing failed pain control. His most recent crisis occurred 11 months before this episode.

Once admitted, the patient’s at-home extended-release oxycodone was supplemented with 1 mg IV hydromorphone every three hours. IV hydromorphone was replaced by a patient-controlled analgesia (PCA) regimen and 0.5 mg boluses of morphine were made available every 15 minutes. This PCA regimen was advanced over the course of admission. Basal morphine delivery was begun and gradually increased. By Hospital Day 10, the patient was receiving 4.0 mg boluses of morphine by PCA available every 15 minutes in addition to basal morphine at 8 mg an hour. Ketorolac was tried briefly and then discontinued because of elevated creatinine. Pregabalin was added twice daily. Extended-release oxycodone 60 mg twice daily was substituted for basal morphine in preparation for discharge; however, the patient’s pain was essentially unchanged, and he had been unable to sleep normally.

The acute pain service was consulted on Hospital Day 11, and with patient consent, a ketamine bolus was administered followed by a low-dose ketamine infusion. The initial bolus of 5 mg ketamine produced immediate analgesia, and the patient reported feeling comfortable for the first time during the admission. The infusion was delivered at 9 mg an hour and increased to 18 mg an hour and then to 24 mg an hour over the following half day.
When the basal rate was increased, bolus doses of ketamine were given: 1 mg was given with the increase to 18 mg an hour and two 5 mg doses were given with the increase to 24 mg an hour. The patient slept eight hours the evening after initiation of ketamine therapy and reported general improvement in his pain. In the 24 hours before ketamine was started, the patient had self-administered 172 mg of morphine by PCA, as opposed to 88 mg of morphine in the 24 hours after ketamine was begun (Fig. 1). Somnolence and horizontal nystagmus occurred immediately after boluses of ketamine and lasted less than 10 minutes. The patient denied hallucinations or disturbing dreams. The ketamine infusion was discontinued on Hospital Day 14, and the patient was discharged on extended-release oxycodone 60 mg twice daily, pregabalin 100 mg twice daily, and oxycodone/acetaminophen for breakthrough pain. On discharge, the patient’s pain was absent in all but one previously affected joint, and thereby greatly diminished. When contacted 10 days after discharge, the patient reported resolution of his shoulder and knee pain, and that he had returned to a preadmission level of chronic pain.

**Comments**

No consensus exists regarding the effective treatment of sickle cell crisis pain. Investigations of this problem have been inconclusive, and comparisons between trials are difficult.\(^1\) We echo the call of other authors for additional research in this field and feel that cautious experimentation with novel agents is appropriate.

Ketamine may be a useful adjunct to traditional opioid regimens for control of sickle cell crisis pain in adults. In this case, we observed instantaneous analgesia with a bolus of ketamine. Relief was sustained with infused ketamine, the patient’s sleep improved, and he demonstrated decreased opioid demand. The patient was able, in three days, to transit to oral medications compatible with discharge. Side effects of ketamine therapy were minimal and predictable.

Because sickle cell pain occurs as repeated bouts of severe nociceptive stimulation on a background of chronic pain, it may both establish opioid dependence and develop a neuropathic component. The latter phenomenon is thought to occur, in part, through sensitization of spinal neurons subjected to repeated noxious stimuli.\(^5,7\) Although the analgesic action of opioids occurs primarily at opioid receptors, opioid tolerance and the development of neuropathic pain both involve activation of NMDA receptors.\(^5,7\) If so, ketamine as an NMDA receptor antagonist may represent a “2-for-1” type intervention, helping to overcome tolerance to opioids as well as attenuating neural sensitization.

We temper our conclusions knowing that ketamine was started late in this patient’s crisis. The perceived effect of ketamine in this case may have been the result, in part, the crisis running its natural course. Also, the brief trial of ketorolac and the initiation of pregabalin may have contributed to the patient’s relief. Nonetheless, our evidence is consistent with the known biochemical activity of ketamine, with a report of ketamine’s utility in managing pediatric sickle cell crises and with

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**Fig. 1.** The total (PCA request plus basal) morphine delivered per hour hospital stay is shown.
ketamine’s reported efficacy in breaking opioid
tolerance.\textsuperscript{2,3,6–9} We also note our success in preventing a third discharge against medical advice, an important marker of sickle cell patient satisfaction.\textsuperscript{10}

Our experience recommends systematic investigation of ketamine’s role in treating adult sickle cell crisis pain. Moreover, comanagement of sickle cell crises by hospitalists and anesthesiologists may improve care. Further investigation is warranted.

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