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Low Dose Ketamine for Opioid Refractory Cancer Pain

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Background

Pain is a common complication for patients with advanced cancer, occuring in up to 90% of patients. Intractable pain has been reported in 10-20% of these patients. Cancer pain is often of mixed etiology and may have nociceptive, neuropathic and inflammatory components. Opioids are frequently prescribed for the management of moderate to severe cancer pain. However, there are instances where opioids and traditional adjuvant medications are not sufficient to control severe cancer pain. Ketamine is being used more frequently in the hospice and palliative setting to control this opioid refractory pain. Unfortunately there is mixed evidence in the literature and there are no widely agreed upon guidelines for dosing.

Objectives

- To describe the successful use of sub-anesthetic ketamine in the management of high dose opioid refractory cancer pain
- To propose a new area of study in the use of sub-anesthetic ketamine for management of an opioid refractory cancer pain

Current HF Policy: Ketamine in ER for Pain

Henry Ford Tier 1 Policy: Utilization of Low Dose Ketamine for Pain Management in Emergency Medicine for Adults (age greater than or equal to 15 years)

IV ketamine as an adjunct analgesic for patients tolerant to opioids or as an alternative to opioids in other acute and chronic pain diagnoses

- Tumor progression, bone metastases
- Spinal or orthopedic surgery, major limb injuries
- Sickle cell disease
- Cluster headaches
- Chronic abdominal pain

Dosage for ketamine IV infusion range from 0.1-0.3 mg/kg, max 30mg.

This is what was utilized as a test bolus for this patient.

Refractory Pain

Opioid refractory cancer pain is thought to be related to the activation of N-methyl-D-aspartate (NMDA) receptors in certain regions of the central nervous system. There is an association with nociceptive activation of the NMDA receptor, clinical hyperalgesia or allodynia and reduced opioid sensitivity. There is growing evidence that the NMDA receptor plays an active role in the development of opioid tolerance. By blocking activated NMDA receptor channels, it is thought that this “resets” the neuronal hyperexcitability and subsequently reduces pain signaling.

Case

A 32 year old male, receiving home hospice, with stage IV gastric adenocarcinoma, complicated by severe cancer-related abdominal pain presented to the ED in a pain crisis, agitated, confused and drowsy. His pain had been managed with a fentanyl PCA at home, with a 650 mcg/hr continuous infusion and a 200mcg demand dose with a 10 minute lockout. His fentanyl use escalated over the preceding days with 31,600 mcg of fentanyl (5266 oral morphine equivalents) in the 24 hours leading up to presentation. In the ED, his fentanyl PCA was continued and he was given hydromorphone 6mg IV and dexamethasone 10mg IV without effect. He was then given a 0.3 mg/kg ketamine bolus with improvement of his pain. He was subsequently admitted to the inpatient hospice unit for further pain management. He was initiated on a low dose ketamine infusion at 0.1mg/kg/hr and was rotated to a hydromorphone PCA at a continuous infusion of 13mg/hr (which is a 25% dose reduction from total fentanyl use) and a 10mg demand dose and 10 minute lockout. His ketamine infusion was titrated upwards to 0.2mg/kg/hr with improvement of his pain. He was maintained at this rate with adequate pain control while his hydromorphone PCA was able to be tapered down to a continuous infusion of 6mg/hr (decreased by 2mg/hr daily) and demand dose of 8mg with a 10 minute lockout. He was subsequently weaned off the ketamine infusion with sustained pain control and a 50% decrease in his opioid requirement. He experienced mild non-disturbing hallucinations and vivid dreams which were adequately controlled with haloperidol and lorazepam. The patient was able to be discharged home with adequate pain control on the hydromorphone PCA with home hospice.

Literature Review

The most recent Cochrane Review for ketamine use as an adjuvant to opioids in the relief of refractory cancer pain concluded that there was insufficient evidence to assess benefits and harms and that more randomized controlled trials examining specific low dose ketamine clinical regimens are needed. There are many case reports supporting its use for this indication. However there are few studies done and results from them are mixed. There was one notable negative study by Hardy et al. which utilized a rapid dose escalation to a dose higher than in most other literature, but showed a sizable placebo effect and low number needed to harm for adverse side effects. The heterogeneous results may be attributed to small sample sizes and differing doses and routes of administration of ketamine. Given the mixed results in the literature, it is likely that certain patients benefit from ketamine, while others do not. Studies have failed to determine any factors associated with a favorable response. No definitive association has been found with age, gender, or pain mechanism. One study showed that most patients who benefitted were using more than one coanalgesic, implying that pain that was less responsive to conventional analgesics was more responsive to ketamine.

Pharmacology of Ketamine

Ketamine is a potent NMDA antagonist, and therefore may reduce opioid tolerance by blocking activation of this receptor. It acts by binding and blocking NMDA receptor channels when they are in the open, activated state as well as binding to a secondary site, which reduces the frequency of channel openings. It is 10-fold stronger than methadone as an NMDA antagonist and exerts its analgesic effects through many other non-NMDA binding sites including muscarinic and nicotinic acetylcholine receptors, voltage-gated calcium channels, D2 dopamine receptors and GABA receptors. In sub-anesthetic doses, the patient remains awake and responsive while experiencing significant analgesia. The IV onset of action is within seconds, and the half-life is 2-3 hours.

Side effects of ketamine include dysphoria, misperceptions, hallucinations, and alterations in body or mood. Sub-anesthetic doses are commonly associated with mild and transient impairments in attention, memory and judgement. These effects can generally be controlled by low doses of benzodiazepine or haloperidol. Mild increases in heart rate or blood pressure can occur. Naloxone does not reverse the analgesic effects or side effects of ketamine.

Proposal for Future Study

Given the mixed results in the literature, it would be beneficial to determine if a certain population of patients would benefit the most from the use of ketamine as an adjunct in the treatment of opioid refractory cancer pain. In order to better identify this population, we propose the use of a test bolus. This could use the bolus infusion described in Henry Ford’s Tier 1 policy for low dose ketamine for pain management in the emergency department. We propose administering this to a patient being considered for ketamine treatment in the setting of a pain crisis. If the patient has a good response to the test bolus, then the patient can be started on a continuous infusion as this may mean it is more likely to be efficacious. We hypothesize that by using this test bolus to select the patient population, this may help yield more definitive results on the utility of ketamine in the treatment of opioid refractory cancer pain and shed some light onto which patients would benefit most.

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