1-26-2022

A Case Report of Subanesthetic Ketamine Bolus and Infusion for Opioid Refractory Cancer Pain

Nicole Forth
Henry Ford Health

Michelle Nguyen
Henry Ford Health, mnguyen3@hfhs.org

Anthony S. Grech
Henry Ford Health, agrech1@hfhs.org

Recommended Citation
Forth N, Nguyen M, and Grech A. A Case Report of Subanesthetic Ketamine Bolus and Infusion for Opioid Refractory Cancer Pain. J Palliat Med 2022.

JOURNAL OF PALLIATIVE MEDICINE
Volume XX, Number XX, 2022

DOI: 10.1089/jpm.2021.0239

A Case Report of Subanesthetic Ketamine Bolus and Infusion for Opioid Refractory Cancer Pain

Nicole Forth, DO,[i] Michelle Nguyen, MD, and Anthony Grech, MD

Abstract

Opioids and traditional adjuvant medications are frequently prescribed for the management of moderate to severe cancer pain with good effect. However, there are many cases, in which patients experience severe opioid refractory cancer pain. Ketamine is being used more frequently in the hospice and palliative setting to manage opioid refractory pain, although high-quality evidence regarding its effectiveness is lacking. It seems certain patients respond favorably to ketamine, while others experience no effect. Studies have not yet identified factors associated with a favorable response to ketamine. We present a case describing the successful treatment of high-dose opioid refractory cancer pain with a subanesthetic ketamine infusion and propose the novel use of a pre-infusion test bolus of ketamine to identify patients who are likely to respond favorably to an infusion.

Keywords: ketamine; opioid refractory cancer pain; test bolus

Introduction

Pain is a common complication for patients with advanced cancer, occurring in up to 90% of patients.[1] Cancer-related pain is often of mixed etiology and may have nociceptive, neuropathic, and inflammatory components. Opioids and traditional adjuvant medications are frequently prescribed for the management of moderate to severe cancer pain; however, these interventions provide insufficient relief in some cases.

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.[1] Nociceptive activation of the NMDA receptor is associated with clinical hyperalgesia, allodynia, and reduced opioid sensitivity.[1] Growing evidence suggests that the NMDA receptor plays an active role in the development of opioid tolerance.[2–10]

Ketamine is a potent NMDA receptor antagonist. By blocking activated NMDA receptor channels, it is thought that ketamine ''resets'' neuronal hyperexcitability and subsequently reduces pain signaling, thus reducing opioid tolerance. Ketamine is not only 10-fold stronger than methadone as an NMDA receptor antagonist but also exerts its analgesic effects through many other non-NMDA-binding sites throughout the central nervous system thought to be involved in pain perception: muscarinic and nicotinic acetylcholine receptors, voltage-gated calcium channels, D2 dopamine receptors, and GABA receptors. In subanesthetic doses of ketamine, the patient remains awake and responsive while experiencing significant analgesia. The intravenous (IV) onset of action is within seconds, and the half-life is ~45 minutes. Side effects of ketamine include dysphoria, misperceptions, hallucinations, and dissociation. Subanesthetic doses are commonly associated with mild and transient impairments in attention, memory, and judgment, which can generally be controlled by low doses of benzodiazepines or haloperidol.[11]

Despite its analgesic potential, there remains a paucity of randomized clinical trials demonstrating the efficacy of ketamine for severe, opioid-refractory pain. Existing studies have provided mixed results regarding analgesic benefit of ketamine for patients with cancer-related pain.[12–26] 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.[26] Many case reports support the use of ketamine for this indication.[27]

However, few formal studies have been done, and results from existing studies are mixed. One notable negative study by Hardy et al. examined a rapid ketamine dose escalation to a dose higher than what has been investigated in most studies and showed a sizable placebo effect and low number

Department of Hospice and Palliative Medicine, Henry Ford Health System, Detroit, Michigan, USA.
[i]ORCID ID (https://orcid.org/0000-0001-6618-0575).
Accepted December 6, 2021.

needed to harm for adverse side effects.[28] The heterogeneous results may be attributed to small sample sizes, differing doses, and routes of ketamine administration.

Given the heterogeneity in the literature, it is reasonable to postulate that there are subgroups of patients who respond to ketamine and others who do not. Or, perhaps there are certain cancer pain syndromes that are more or less amenable to ketamine. We are not aware of any studies that have identified patient factors or characteristics associated with favorable response to ketamine. The ability to identify patients who are more likely to have a favorable response would allow clinicians to more rapidly achieve pain control in responders and avoid risk of side effects in nonresponders.

We present the case of a patient with opioid refractory cancer pain who was treated with a test bolus of low-dose ketamine before initiating a subanesthetic ketamine infusion. The test bolus dose used for this patient was derived from the Henry Ford Policy: Utilization of Low-Dose Ketamine for Pain Management in Emergency Medicine for Adults (age older than or equal to 15 years).[29] The policy recommends an IV ketamine bolus range of 0.1 to 0.3 mg/kg (max 30 mg) as an adjunct analgesic for patients who are tolerant to opioids or as an alternative to opioids in other acute and chronic pain diagnoses, including tumor progression, bone metastases, spinal or orthopedic surgery, major limb injuries, sickle cell disease, cluster headaches, and chronic abdominal pain.[29]

As this patient experienced pain relief with the bolus dose, we felt that he would benefit from initiation of a continuous infusion of subanesthetic ketamine. We believe that this case highlights a potential means of identifying patients who are more likely to benefit from subanesthetic ketamine infusions for opioid refractory cancer pain.

Case Description

A 32-year-old man receiving home-hospice care with stage IV gastric adenocarcinoma presented to the emergency department (ED) in a pain crisis with agitation, confusion, and drowsiness. The patient suffered from chronic abdominal pain related to his known cancer burden throughout the small bowel and omentum that had been well-controlled since his initial enrollment with hospice 8 weeks before presentation with a fentanyl citrate patient-controlled analgesia (PCA) at home. His wife reported 1–2 weeks of progressive abdominal pain despite adjustments to his PCA to the settings on presentation of 650-mcg/h continuous infusion and a 200-mcg demand dose with a 10-minute lockout.

Upon interrogation of his pump on presentation, it was discovered that his fentanyl use had escalated over the preceding days with 18,400 mcg of fentanyl citrate, or 3066 oral morphine equivalents (OME) two days before presentation, and with 31,600 mcg of fentanyl citrate, or 5266 OME, in the 24 hours leading up to presentation. Of note, his wife also reported administering lorazepam sublingual 1 mg and haloperidol of unknown dose and frequency at home for at least two days before presentation in an attempt to alleviate his pain and agitation without effect.

On examination, the patient was described as restless, disoriented to the situation, and unable to appropriately answer questions. His abdomen was described as nondistended, diffusely tender to palpation, with bowel sounds present. There was notably no mention of myoclonus or seizure-like activity that may have raised concern for opioid-induced neurotoxicity. In the ED, his fentanyl PCA was maintained with registered nurse (RN) as-needed boluses in the setting of his altered mentation, and he was given hydromorphone hydrochloride IV 6 mg and dexamethasone IV 10 mg without effect in his pain.

One hour and 21 minutes after he received the IV hydromorphone, he was given a 0.3 mg/kg ketamine hydrochloride bolus with improvement noted in his pain. This was chosen as the bolus dose as opposed to a lower dose due to the severity of the patient's pain and his younger age. IV methadone could also have been considered here as an alternative to the ketamine bolus, although this was not available on our hospital formulary at the time.

Success of the ketamine bolus was determined based on both his documented Pain Assessment in Advanced Dementia Scale (PAINAD) scores from a maximum score of 10 before his ketamine bolus, to a score of 7 approximately four hours after the ketamine bolus (PAINAD scores had remained 10 after administration of the hydromorphone and dexamethasone), as well as subjective data from both the patient's wife stating ''patient improved most following the ketamine bolus,'' and bedside RN documentation noting that ''Patient does appear to be less symptomatic'' following the ketamine bolus. The PAINAD scale was initially utilized given his encephalopathy on presentation. Of note, the patient received a single dose of haloperidol IV 2 mg for agitation on the evening of admission, approximately seven hours after he received the initial ketamine bolus. He did not receive any additional haloperidol throughout the rest of his hospitalization.

He was subsequently admitted to the inpatient hospice unit for further pain management. He was then initiated on a low-dose ketamine hydrochloride infusion at 0.1 mg/kg/h and was rotated to a hydromorphone hydrochloride PCA at a continuous infusion of 13 mg/h (a 25% dose reduction from total fentanyl use) and a 10 mg demand dose with a 10-minute lockout. Upon reassessment later in the evening on the day of admission, the patient appeared uncomfortable; thus, his ketamine infusion was titrated upward to 0.2 mg/kg/h with improvement of his pain.

By the following morning, the patient was alert and participating in conversations, and was able to ''state his pain was 'okay' and that he did not need an additional as needed dose at this time.'' His wife reported to the hospice team that the patient slept well overnight for the first time in two years. He was maintained at this ketamine infusion rate with adequate pain control while his hydromorphone PCA was tapered down over a period of 4 days to a continuous infusion of 6 mg/h and demand dose of 8 mg with a 10-minute lockout.

Of note, the patient experienced restlessness and impulsiveness throughout his hospital course, which were initially treated with lorazepam 1 mg IV every eight hours scheduled plus 2 mg IV every two hours, as needed. Approximately halfway through his hospital course, this was adjusted to his discharge regimen of lorazepam 1 mg IV every morning, 1 mg IV every afternoon, and 2 mg IV nightly. He also experienced mild nondisturbing hallucinations and vivid dreams that did not require any additional treatment.

He was subsequently weaned off the ketamine infusion 6 days after admission with sustained pain control and a 50%

decrease in his opioid requirement, from 5266 OME on presentation to 2600 OME before discharge (Fig. 1). The patient discharged home with adequate pain control on the hydromorphone PCA with home hospice care. His pain control was reportedly maintained until his death 13 days after discharge.

Discussion

Our case supports the utility of subanesthetic ketamine for opioid refractory cancer pain. In addition, it highlights a preinfusion subanesthetic ketamine bolus as a potential method of identifying patients who are likely to respond favorably to a subanesthetic ketamine infusion. IV ketamine's onset of action is within seconds with a half-life in the 45-minute range. These properties allow a bolus to quickly identify response to ketamine, and for patients who respond, it provides long enough relief to bridge until the subanesthetic infusion is available.

This patient appeared to respond favorably to ketamine with regard to pain with minimal adverse effects. The patient and his wife did report occasional hallucinations that were possibly related to the ketamine infusion versus high-dose opioids that were eventually decreased, although these hallucinations were nondisturbing and gradually improved. He initially presented encephalopathic and disoriented and was unable to participate in questioning. By the following morning, <24 hours after the initial ketamine bolus, he was alert and answering questions appropriately. The timing of the resolution of his encephalopathy appeared to correlate with improvement in his pain.

It should be noted and considered that this patient's pain crisis was purely the result of opioid hyperalgesia given the high doses used and rapid escalation in the days leading up to his inpatient admission. An argument can be made that the improvement in his pain is explained by opioid rotation and dose reduction alone. In this case, however; we feel the patient's improvement in pain is better explained by ketamine given the initial favorable response after ketamine bolus which was administered before an opioid rotation.

Another major point of consideration is the use of possible confounding adjunctive medications in the treatment of this patient's pain. The concept of total pain involves addressing not only a patient's physical pain, but also their psychological, spiritual, and social needs. Benzodiazepines and antipsychotics are frequently utilized in palliative and hospice care for the treatment of symptoms relating to a patient's emotional or psychological state if felt to be contributing to their total pain. This patient was receiving lorazepam and haloperidol of unknown amounts for at least two days before this presentation, and while he only received one dose of haloperidol for agitation after presentation, he was consistently given scheduled IV lorazepam throughout his hospitalization for ongoing restlessness and impulsiveness, which certainly could have resulted in improvement in his total pain if a psychological aspect was contributing.

However, we do feel that the majority of his pain was truly physical in relationship to his known cancer burden, as it is worth noting that he had never expressed any prior issues with emotional or spiritual distress during his outpatient visits to the palliative care office in the few months preceding his death, although this could have changed as he entered the final days and weeks of life.

In conclusion, we hypothesize that a subanesthetic ketamine bolus can be used as a method to identify patients with opioid refractory cancer pain who are likely to benefit from a subanesthetic ketamine continuous infusion. Our case offers one example of the successful implementation of this approach, although future studies are needed to better investigate the effectiveness of a preinfusion ketamine bolus. Although ideal, a blinded randomized controlled trial would likely not be feasible due to ethical issues pertaining to the care of patients at the end of life. Alternatively, case control studies involving patients with opioid refractory cancer pain

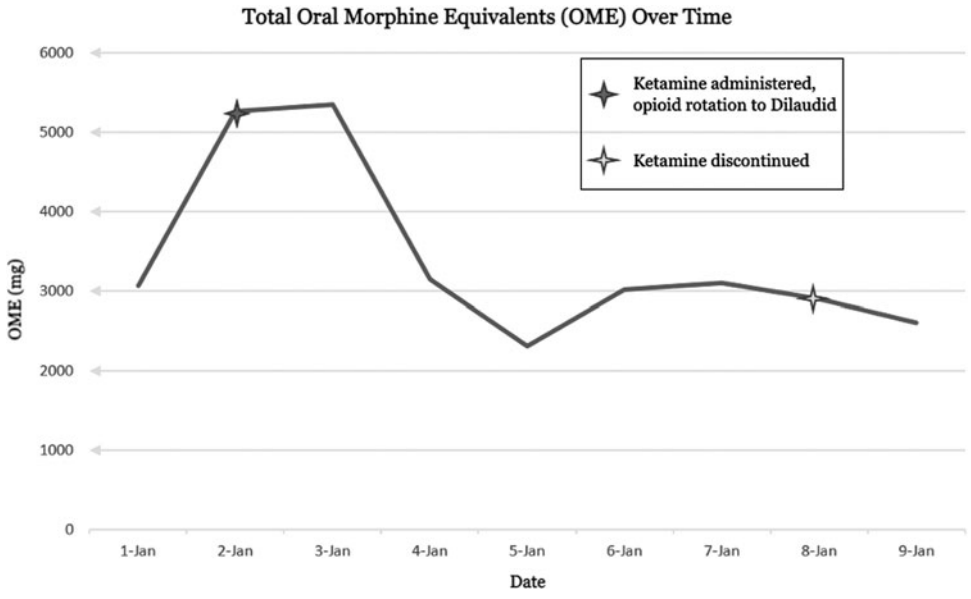

FIG. 1. Total opioid requirements (converted to OME) throughout the patient's hospitalization, pre- and postketamine administration. OME, oral morphine equivalents.

may be a good option. We recommend inclusion criteria as patients with cancer pain uncontrolled with opioids with and without adjunctive medications.

It would be helpful if all adjuncts were already at what is considered to be a therapeutic dose and duration before initiating ketamine to avoid a possible confounder of the adjunct simply not yet reaching therapeutic potential. We recommend exclusion criteria as patients with contraindications to ketamine, such as those with schizophrenia or other psychoses, or dementia, due to the possibility of the adverse effect of vivid dreams/hallucinations causing increased agitation in these populations. This case adds important data to the evidence base for subanesthetic ketamine for opioid refractory cancer pain and offers direction for future studies.

Acknowledgments

This material is the result of work supported with resources and the use of facilities at Henry Ford Hospital, Detroit, MI. The authors thank Karla D. Passalacqua, PhD, at Henry Ford Hospital for editorial assistance.

Funding Information

No funding was received for this article.

Author Disclosure Statement

No competing financial interests exist.

References

1. Loveday B, Sindt J: Ketamine protocol for palliative care in cancer patients with refractory pain. J Adv Pract Oncol 2015;6:555–561.
2. Garzon J, Rodriguez-Munoz M, Sanchez-Blazquez P: Direct association of Mu-Opioid and NMDA glutamate receptors supports their cross-regulation: Molecular implications for opioid tolerance. Curr Drug Abuse Rev 2012;5. [Epub ahead of print]; DOI: 10.2174/1874473711205030199.
3. Trujillo KA, Akil H: Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science 1991;251:85–87.
4. Mao J, Price DD, Mayer DJ: Mechanisms of hyperalgesia and morphine tolerance: A current view of their possible interactions. Pain 1995;62:259–274.
5. Mayer DJ, Mao J, Price DD: The association of neuropathic pain, morphine tolerance and dependence, and the translocation of protein kinase C. NIDA Res Monogr 1995;147: 269–298.
6. Sánchez-Blázquez P, Rodríguez-Muñoz M, Garzón J: Mu-opioid receptors transiently activate the Akt-nNOS pathway to produce sustained potentiation of PKC-mediated NMDAR-CaMKII signaling. PLoS One 2010;5: e11278.
7. Garzón J, Rodríguez-Muñoz M, Sánchez-Blázquez P: Do pharmacological approaches that prevent opioid tolerance target different elements in the same regulatory machinery? Curr Drug Abuse Rev 2008;1:222–238.
8. Garzón J, Rodríguez-Muñoz M, Vicente-Sánchez A, et al.: RGSZ2 binds to the neural nitric oxide synthase PDZ domain to regulate mu-opioid receptor-mediated potentiation of the N-methyl-D-aspartate receptor-calmodulin-dependent protein kinase II pathway. Antioxid Redox Signal 2011;15:873–887.
9. Rodríguez-Muñoz M, Sánchez-Blázquez P, Herrero-Labrador R, et al.: The σ1 receptor engages the redox-regulated HINT1 protein to bring opioid analgesia under NMDA receptor negative control. Antioxid Redox Signal 2015;22:799–818.
10. Rodríguez-Muñoz M, Garzón J: Nitric oxide and zinc-mediated protein assemblies involved in mu opioid receptor signaling. Mol Neurobiol 2013;48:769–782.
11. Rosenbaum SB, Gupta V, Palacios JL: Ketamine. [Updated 2021 Feb 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2021.
12. Nesher N, Serovian I, Marouani N, et al.: Ketamine spares morphine consumption after transthoracic lung and heart surgery without adverse hemodynamic effects. Pharmacol Res 2008;58:38–44.
13. Chumbley GM, Thompson L, Swatman JE, et al.: Ketamine infusion for 96 hr after thoracotomy: Effects on acute and persistent pain. Eur J Pain 2019;23:985–993.
14. Herring AA, Ahern T, Stone MB, et al.: Emerging applications of low-dose ketamine for pain management in the ED. Am J Emerg Med 2013;31:416–419.
15. Kator S, Correll DJ, Ou JY, et al.: Assessment of low-dose i.v. ketamine infusions for adjunctive analgesia. Am J Health-Syst Pharm 2016;73(suppl 1):S22–S29.
16. Beaudoin F, Lin C, Guan W, et al.: Low-dose ketamine improves pain relief in patients receiving intravenous opioids foracute pain in the emergency department: Results of a randomized, double-blind, clinical trial. Acad Emerg Med 2014;21:1194–1202.
17. Miller J, Schauer S, Ganem V, et al.: Low-dose ketamine vs morphine for acute pain in the ED: A randomized controlled trial. Am J Emerg Med 2015;33:402–408.
18. Motov S, Rockoff B, Cohen V, et al.: Intravenous subdissociative-dose ketamine versus morphine for analgesia in the emergency department: A randomized controlled trial. Ann EM 2015;66:222–229.
19. Sin B, Ternas T, Motov S: The use of subdissociative-dose ketamine for acute pain in the emergency department. Acad Emerg Med 2015;22:251–257.
20. Ahern T, Herring A, Stone M, et al.: Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain. Am J Emerg Med 2013;31: 847–851.
21. Yeaman F, Meek R, Egerton-Warburton D, et al.: Subdissociative-dose intranasal ketamine for moderate to severe pain in adult emergency department patients. Emerg Med Australasia 2014;26:237–242.
22. Ahern T, Herring A, Anderson E, et al.: The first 500: Initial experience with widespread use of low-dose ketamine for acute pain management in the ED. Am J Emerg Med 2015;33:197–201.
23. Lester L, Braude D, Niles C, et al.: Low-dose ketamine for analgesia in the ED: A retrospective case series. Am J Emerg Med 2010;28:820–827.
24. Richards J, Rockford R: Low-dose ketamine analgesia: Patient and physician experience in the ED. Am J Emerg Med 2013;31:390–394.
25. Goltser A, Soleyman-Zomalan E, Kresch F, et al.: Short (low-dose) ketamine infusion for managing acute pain in the ED: Case-report series. Am J Emerg Med 2015;33: 601.e5–601.e7.
26. Bell RF, Eccleston C, Kalso EA: Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev 2017;2017:CD003351.

27. Waldfogel J, Nesbit S, Cohen S, et al.: Successful treatment of opioid-refractory pain with short-course, low dose ketamine. J Pain Palliat Care Pharmacol 2016;30:4, 294–297.
28. Hardy J, Quinn S, Fazekas B, et al.: Randomized, double-blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain. J Clin Oncol 2012;3611–3617.
29. Utilization of Low Dose Ketamine for Pain Management in Emergency Medicine. https://henryford-henryfordhospital.policystat.com/policy/6962441/latest (Last accessed June 1, 2021).

Address correspondence to:
Nicole Forth, DO
Department of Hospice and Palliative Medicine
Henry Ford Health System
Detroit, MI 48202
USA

E-mail: nforth1@hfhs.org