



# Low-dose ketamine as an adjuvant for pain control in a cancer patient: a case report

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**Abstract:** Cancer patients often suffer from pain related problems such as under-treatment of pain, ineffective and persistent opioid administration as well as adverse opioid use outcomes. There is a growing need for non-opioid analgesic alternatives for patients undergoing treatment for obstinate pain. Ketamine is a fast-acting N-methyl-D-aspartate (NMDA) receptor antagonist that has been emerging as an effective medication for pain alleviation. While protocols have been established for the use of Low-Dose Ketamine (LDK) for post-operative pain, there is growing evidence for using LDK as a clinical alternative to opioids in a palliative care setting. This case study involves monitoring the efficacy of LDK treatment in combination with opioid analgesics in a cancer patient in a hospital setting. This is a very selected case of a patient with Metastatic Prostate Cancer (Gleason 9 Adenocarcinoma) where LDK was shown to be efficacious at reducing pain when opioids and standard pain medications were not satisfactory. While the study involved using a relatively novel pharmacological protocol and close patient monitoring, the patient reported a sustained reduction in pain level based on the Numerical Rating Scale for months after the termination of LDK infusions. Moreover, the treatment also resulted in a reduction of total opioid usage after the addition of LDK. Although additional research is needed to ascertain optimal dosing schedules and route of Ketamine, given these promising findings, Ketamine may be a useful option for improving the treatment of refractory pain in patients with cancer and a good tool in palliative medicine for treating neoplastic pain.

**Keywords:** Low-dose ketamine (LDK); palliative care; neoplastic pain; cancer; case report

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## Introduction

Pain is the most common symptom for patients diagnosed with cancer; the World Health Organization (WHO) cites that 55–66% of cancer patients experienced greater than moderate pain despite treatment in a pain management unit (1). While opioids remain to be the mainstay of cancer pain treatment, patients on these medications endure exacerbating side effects and complications. Additionally, due to opioid tolerance, or reduced responsiveness, 10-fold increases in opioid

doses are common in chronic pain management (2). This rapid increase in dosages is problematic due to the narrow therapeutic range of opioids and their high-risk side effects, such as nausea/vomiting, constipation, sedation, drowsiness, and neurological effects such as neuroexcitation, myoclonus, and urinary retention (3,4). The need for non-opioid treatment options for patients undergoing acute, chronic and obstinate pain is of great importance; one alternative is low-dose ketamine (LDK) infusion.

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**Table 1** Patient total opioid usage (opioid oral MME) averaged (I) 30 days before LDK infusion, (II) during LDK infusion, (III) 30 days after ketamine infusion. Opioid oral MME was calculating by taking the average total daily dose of a drug and multiplying it by a drug-specific conversion factor. The conversion factors that were used are as following: Hydromorphone, IV [20]; Oxycodone, PO [1.5]; Fentanyl, Transdermal Patch [2.4]; Methadone, PO {1–20 mg [4], 21–40 mg [8], 41–60 mg [10], > 61 mg [12]}

Relation to ketamine infusion [6/21–6/23]	Opioid medication	Opioid strength	Total MME per day
(I) Before ketamine infusion	Oxycodone	60 mg PO	458.8
	Hydromorphone	5 mg IV	
	Fentanyl	12 mcg/hr Patch	
	Methadone	30 mg PO	
(II) Ketamine infusion	Oxycodone	25 mg PO	677.5
	Hydromorphone	2 mg IV	
	Fentanyl	0	
	Methadone	60 mg PO	
(III) After ketamine infusion	Oxycodone	60 mg PO	310
	Hydromorphone	1 mg IV	
	Fentanyl	0	
	Methadone	25 mg PO	

MME, morphine milligram equivalent; LDK, low-dose ketamine.

Here we report a case with Metastatic Prostate Cancer (Gleason 9 Adenocarcinoma), where LDK was used following an initial opioid-based pain management treatment to better manage pain and reduce complications from high-dose opioid use. We present the following article in accordance with the CARE Reporting Checklist (available at <http://dx.doi.org/10.21037/apm-20-1685>).

## Case presentation

The current case study received approval from the institutional review board. The patient, a 55-year-old male, presented with a 2-year history of Metastatic Prostate Cancer (Gleason 9 Adenocarcinoma) and was referred to the palliative care for secondary unmanageable lower back pain and local hip pain. The etiology of the neuropathic and somatic pain was from bone metastasis that was confirmed with imaging studies. The patient had a history of atrial fibrillation with a rapid ventricular response, dyslipidemia, hypertension, obesity, heart palpitations, sleep apnea, stroke, as well as prostate cancer which metastasized to the bone. The patient was prescribed a myriad of medications including Atorvastatin (Lipitor), Bisacodyl (Dulcolax), Gabapentin, Metoprolol (Toprol XR), as well as several opioid painkillers, such as fentanyl, oxycodone, and

hydromorphone. The use of NSAIDs such as Ketorolac was limited due to the potential onset of GI bleeding and acute renal failure. The patient also had recurring issues with constipation, a likely side effect of the opioid medications he was taking. As a result of the opioid-induced constipation, the patient was given a bowel regimen of Senna 8.6 mg PO nightly, Miralax 17 g POM daily, Bisacodyl suppository and tablet 10 mg, and Dexamethasone 6 mg PO daily.

The main criteria used to assess the patient's pain was the Numerical Rating Scale (NRS), which was incorporated into the Physical Exam. The patient consistently reported a 9/10 on the NRS as well as frequent bouts of constipation. An obvious diagnostic challenge faced during the study was the subjective nature of the NRS.

The patient was receiving 458.8 morphine milligram equivalents (MME) per day (*Table 1*); however, was still reporting an average pain of 9/10 on the NRS. Clinical judgement for the patient was to not drastically increase the patient's opioid usage due to present adverse effects, such as nausea, constipation, urinary retention, lethargy, and ascending drug tolerance. To avoid undesirable effects of high dosage opioids, patient was considered for the LDK infusion. The patient under observation was deemed to have been on the maximum dosages of certain opioids and was at risk of acquiring opioid-induced hyperanalgesia.

**Table 2** Institutional LDK intravenous medication administration guidelines illustrating the proper use of the pharmacotherapy approved for pain management in this patient

Medication	IV push		Continuous infusion		Administration considerations	Pharmacy stability
	Dilution (max push dose)	Locations	Standard concentration	Locations		
Ketamine (Ketalar)	50 mg/mL over 1 minute	ED, Critical Care, SDU, OR, PACU, Cardiology, Cath Lab, End of Life	D5W 100 mg in 100 mL 1 mg/mL	All	Close monitoring required during administration	Use immediately Infusion is stable at room temperature for 24 hours

LDK, low-dose ketamine.

As a result, LDK infusions were deemed appropriate and potential benefits were clearly observed in this case.

A local LDK infusion protocol has been established in 2019 under federal and institutional guidelines and allowed the use of intravenous LDK titration (<0.5 mg/kg) as an adjunct to opioid treatment (*Table 2*). Under these guidelines, the standard concentration of the continuous infusion of Ketamine (Ketalar) was 100 mg in dextrose 5% 100 mL (1 mg/mL) with the maximum push dose being 50 mg/mL over 1 minute. The 3-day infusion was doses as following: 0.1 mg/kg/hr on Day 1, followed by 0.2 mg/kg/hr on Day 2, followed by 0.3 mg/kg/hr on Day 3 (*Figure 1*) (5-8).

Observational data was collected within the first 24 hours of LDK infusion regarding pain characteristics, pain score assessment, vitals, respiratory depression, tolerance and overall satisfaction. The pain intensity and regular opioid dose before starting and upon stopping Ketamine infusion was also compared for 30 days. Additionally, the NRS was routinely monitored every 4 hours while the patient was on the LDK infusion (*Figure 1*). Prior to undergoing the LDK infusion, the patient reported a pain level of 9 on the NRS, with 10 being identified as “maximal pain”. Despite being in substantial pain, the patient was undergoing Palliative Care treatment of the Equianalgesic Dose of 458.8 MME. After 3 subsequent daily infusions, the patient had experienced a daily alleviation of pain to the level of 5 on the NRS. These results manifested alongside a 32.43% reduction in opioid usage. The most significant results were evident further after the termination of the Ketamine Infusion. Over a period of 30 days following the Ketamine Infusion, the patient reported an average pain level of 4.75 on the NRS, an approximately 50% reduction in pain from the start of the Ketamine Infusion. The patient was closely monitored for ketamine side effects, especially within the first hour following each infusion. Common side effects include hallucinations and feelings of agitation; however, the patient did not report any of these adverse effects. On the other

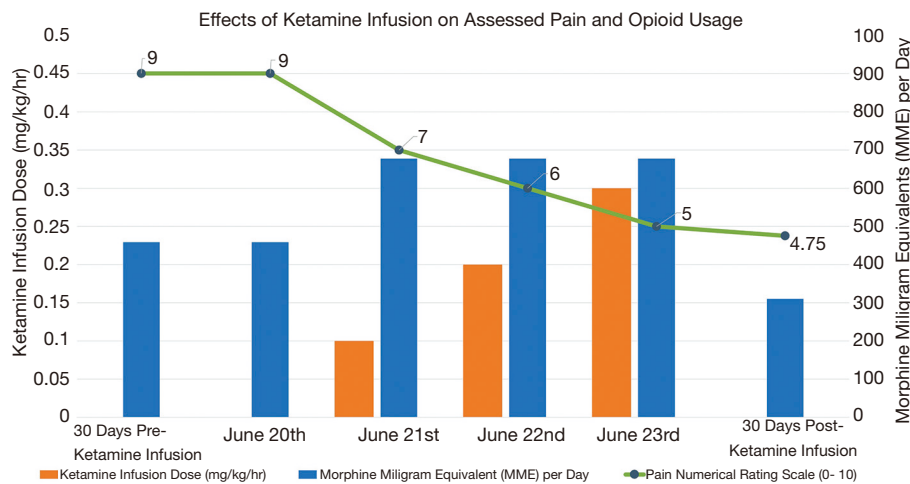
hand, the patient reported feeling less total pain following LDK administration. Additionally, opioid usage dropped to 310 MME a 16.67% drop in Methadone use and a complete termination of Fentanyl use.

Overall, the results obtained point toward the effectiveness of LDK infusions in a Palliative Care setting. These infusions not only alleviated symptoms of pain, but also allowed for a reduction in the use of opioids, and alleviation of possible opioid dependence and associated side effects. No additional adverse events were noted.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Due to the fact that the patient under observation had passed away, informed consent was unable to be obtained. Patient's next of kin were untraceable despite the authors' great efforts to obtain their consent.

## Discussion

Onset of acute pain is a significant issue at all points of the cancer continuum and can occur because of malignant conditions or the treatment plan. Earlier studies confirm that more than 50% of all patients with cancer experience moderate to severe pain (9). The prevalence of pain in cancer survivors is estimated to be 40%, while close to two-thirds of those with advanced disease live with pain (10). Cancer pain management, an often-neglected component of oncological care, is closely associated to the development of the modern hospice measures, and palliative care (11). Additionally, the levels of pain experienced are often difficult to assess due to concerns of patients. In a study involving cancer patients (n=270), difficulty in properly medicating patients was found to be from patient concerns including fear of addiction, reluctance to complain, and side effects of medications (12).



**Figure 1** Patient's daily pain numerical rating scale recorded alongside (I) LDK infusion dose and (II) opioid usage. Prior to undergoing LDK infusion, the patient was experiencing consistent levels of high pain, averaging between 8–9 on the Pain Numerical Rating Scale. Upon administration on the LDK infusion, the patient's pain has dropped significantly and averaged between 4–5 on the Pain Numerical Rating Scale for weeks following the treatment. Additionally, the patients need for opioids has decreased dramatically. LDK, low-dose ketamine.

Cancer patients are frequently resorted to opioid use for pain management. These patients may suffer from under-treatment for their pain and/or adverse opioid use outcomes including unnecessary and persistent opioid use (13,14). Moreover, patients with cancer-related pain are underrepresented in the opioid literature despite high opioid exposure (15). While progress has been made in the management of cancer pain, under-treatment persists and does have significant negative impacts on the quality of life of patients (16). The need for non-opioid analgesics for patients undergoing treatment for acute, chronic, and obstinate pain, calls for safer and more efficacious alternatives.

This report illustrates the potential benefits of using ketamine as an adjunct to high dose opioid usage in the palliative care setting. The patient under observation was dealing with metastatic prostate cancer which had spread throughout his pelvic bones. There were multiple fractures seen on CT on 9/21/2019, indicating the severity of the metastatic disease. The patient, prior to receiving LDK infusions for a 5-day period, was progressively noted to have dampened spirits due to the disease and poor prognosis. The patient, prior to having cancer, was a very active and enthusiastic individual; the inability to participate in sports such as hiking depressed the patient's mood immensely. A hospital note written by one of the nurses after the LDK infusion mentioned that the patient was in "great spirits", portraying the potential benefit of low-dose ketamine in palliative care settings. Ketamine has been shown to have

anti-depressive actions in addition to its ability to relieve pain. An interesting question then arises as to whether Ketamine's actions on NMDA receptors specifically target physical pain, or whether there is an emotional component to its analgesic effect, as well.

Ketamine is a well-known N-methyl-D-Aspartate (NMDA) receptor antagonist, and its analgesic effect is attributed by blocking NMDA receptor induced pain sensitization. Ketamine induces analgesia by prolonging the effect of opioid stimulation by improving the sensitization of opioid receptors (17). There is increasing evidence that LDK has been progressing as a relatively simple, reliable and robust pain reliever in various painful conditions (15-17). The majority of cancer patients with advanced disease have severe pain which significantly impairs health-related quality of life (18). Despite the current emphasis on multimodal analgesic therapy, the potential treatment for pain almost always includes opioids when dealing with advanced stage cancer patients. Given the side effects and dependency issues, there is a strong need of alternate medications. Recent studies have shown that LDK as an adjuvant to opioids significantly reduces the intensity of pain in cancer patients (19,20). The data from these cancer pain control studies exhibit few subjects and involve heterogeneous interventions and outcome measures assessed by different pain assessment tools. Additionally, LDK titrated dose trials are still needed in multiple pain scenarios before it can be declared as a safe analgesic.

## Conclusions

Cancer pain management, an often neglected component of oncological care, is closely associated to the development of modern hospice measures and palliative care. Cancer patients are frequently resorted to opioid use for pain management, sometimes suffering from under-treatment for their pain and/or adverse opioid use outcomes, including unnecessary and persistent opioid use. This is a very selective case of a patient where LDK infusion was shown to be efficacious at reducing pain when opioids and standard pain medications were not satisfactory. While ketamine use in managing post-operative pain is common, LDK infusion (<0.5 mg/kg) also shows further potential to deliver excellent outcomes in pain management for cancer patients while simultaneously curbing the myriad of potential side effects of opioids through minimizing their usage. Although additional research is still required to determine the efficacy, optimal dosing schedules, administration routes of LDK infusion, it is hard to underscore the untapped potential of this new treatment in palliative medicine.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki

Declaration (as revised in 2013). Due to the fact that the patient under observation had passed away, informed consent was unable to be obtained. Patient's next of kin were untraceable despite the authors' great efforts to obtain their consent.

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