Peer review file

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Reviewer A

Comment: This case report demonstrates the use of ketamine on pain control in cancer patients under palliative care. The topic is of interest to physicians working in the field of cancer supportive care, as ketamine has been used in our practice for controlling pain for a long period of time, but so far there has not been any concrete or sufficient evidence to support its use, results from various studies had appeared to be very variable, or even contradictory.

Reply: **As a whole, 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 following a few days of 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.**

Changes in the text: **Page 6, Line 7 to Page 6, Line 19**

Comment: My main issue with this case report is its uniqueness and its added value to the scientific literature. A number of retrospective studies have already been published reporting the use of ketamine as an adjuvant to opioids for refractory cancer pain, illustrating its safety and efficacy, and the potential of reducing opioid doses and minimizing opioid side effects. The authors should be able to specifically point out what is unique about the current reported case and what we can learn from the case.

Reply: **The paper describes the many challenges physicians and patients, consequently,**

face in the palliative care setting. One of these issues is the use of opioids and their numerous adverse effects. The patient under observation was deemed to have been on the maximum dosages of certain opioids and was under risk of acquiring opioid-induced hyper-analgesia. As a result, LDK infusions were deemed appropriate and potential benefits were clearly observed in this case.

Changes in the text: **Page 3, Line 19 to Page 3, Line 22 + Page 6, Line 7 to Page 6, Line 19**

Listed below are some comments and questions.

Case presentation

Comment 1: What is the rationale of using multiple similar opioids together (fentanyl, oxycodone and hydromorphone)?

Reply 1: **The patient was already taking high doses of methadone and other analgesics were added to attempt to alleviate the pain associated with the metastatic prostate cancer. Unfortunately, these attempts were futile, only adding side effects such as nausea, constipation, urinary retention, lethargy, and others while failing to relieve the symptoms of pain.**

Changes in the text: Page 2, Line 7 to Page 2, Line 12 + Page 3, Line 16 to Page 3, Line 18

Comment 2: Which specific pain assessment scale was used? Was it numerical rating scale (NRS)?

Reply 2**: Yes -- the Numerical Rating Scale was used in this case report. All mentions of "Pain Assessment Scale" have been replaced with Numerical Rating Scale (NRS) to better relay the specific parameters that were used in this case.**

Changes in the text: Page 3, Line 11 to Page 3, Line 14

Comment 3: Pain is a subjective symptom; thus pain assessment is bound to be subjective. The pain assessment scale itself does not contain any intrinsic meaning, patients may interpret measurement scales very differently when reporting pain, thus making the baseline scores widely variable between individuals. However, by calculating the raw change or percent change, the measures of improvement are already adjusted for the individual's baseline. Moreover, a significant reduction of opioid dose was reported here, which was an objective outcome.

Reply 3: **The subjectivity associated with the Numerical Pain Rating Scale are mentioned in the 2nd paragraph of the "Case Presentation". We state, "An obvious diagnostic challenged faced during the study was due to the subjective nature of the NRS. A "direct" measure of pain was not conducted and therefore, reliance on the patient's relative interpretation of his pain was the main determinant for the study." Additionally, the "percentage change" relative to the patient's baseline are reported in the 4th paragraph of the "Case Presentation".**

Changes in the text: **Page 3, Line 11 to Page 3, Line 14 + Page 4, Line 18 to Page 4, Line 20**

Comment 4: What was the nature of the pain? Was there any neuropathic component?

Reply 4: **The pain was both neuropathic and somatic in nature. The pain's etiology was from bone metastasis that was confirmed with imaging studies. Additionally, while the patient described the pain as generalized, it was significantly more pronounced to localized areas such as the hip and lower back; there were also the areas of metastasis. To better describe the nature and etiology of the pain, we wrote, "The etiology of the neuropathic and somatic pain was from bone metastasis that was confirmed with imaging studies."**

Changes in the text: **Page 2, Line 22 to Page 2, Line 23**

Comment 5: The pain was described to be "generalised". What was the cause of the pain? Was it related to the underlying cancer condition?

Reply 5: **The pain was both neuropathic and somatic in nature. The pain's etiology was from bone metastasis that was confirmed with imaging studies. Additionally, while the patient described the pain as generalized, it was significantly more pronounced to localized areas such as the hip and lower back; there were also the areas of metastasis. To better describe the nature and etiology of the pain, we wrote, "The etiology of the neuropathic and somatic pain was from bone metastasis that was confirmed with imaging studies."**

Changes in the text: **Page 4, Line 30 to Page 5, Line 2**

Comment 6: Concerning the constipation that the patient had experienced, had laxatives been prescribed and what was the effect?

Reply 6: **Yes -- in fact the patient was put on a specific bowel regimen as a result for opioid-**

induced constipation. The bowel regimen included Senna 8.6 mg PO nightly, Miralax 17g POM daily, Bisacodyl suppository and tablet 10 mg, and Dexamethasone 6 mg PO daily.
Changes in the text: **Page 3, Line 6 to Page 3, Line 10**

Comment 7: A baseline oral morphine equivalent dose of ~83 mg was not a high dose. Ketamine was usually reserved for those with refractory, severe pain.
Reply 7: **The patient was receiving 458.8 morphine milligram equivalents (MME) per day. While this information can be seen in Table 1, the patient was receiving the following medications on a daily basis prior to the LDK infusion: Hydromorphone 5 mg IV, Methadone 30 mg PO, Oxycodone 60 mg PO, Fentanyl 12 mcg/hr patch.**
Changes in the text: **Page 3, Line 15 to Page 3, Line 18 + Table 1**

Comment 8: Concerning the definition of LDK, by <0.5 mg/kg, did you mean 0.5 mg/kg/hr?
Reply 8: **Yes-- this is correct. The units have been adjusted to read "0.5 mg/kg/hr".**
Changes in the text: **Page 4, Line 2 + Page 7, Line 19**

Comment 9: Was the patient also monitored for ketamine side effects?
Reply 9: **The patient was closely monitored for ketamine side effects, especially within the first hour following 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.**
Changes in the text: **Page 4, Line 20 + Page 5, Line 1**

Comment 10: "One month after the initial ketamine infusion, the patient reported a pain level of ~4.75 on the pain assessment scale." How was the pain assessment done at 30 days after ketamine administration? Was this a mean pain score such that it was not an integer?
Reply 10: **The reported pain of 4.75 on the Numerical Rating Scale was a combined average of all recorded pain data during the 30 days following the ketamine infusion. The statement has been changed to illustrate this in a clearer manner. The revised statement reads, "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."**
Changes in the text: **Page 4, Line 18 to Page 5, Line 1 and Figure 1**

Conclusion

Comment 1: Here LDK was referred to as <1 mg/kg, which was different from the "<0.5 mg/kg" mentioned above in the case presentation?

Reply 1: **While different sources define LDK with different parameters, < 0.5 mg/kr/hr remains to be the standard definition of "Low-Dose Ketamine". As a result, we have adapted this to read " < 0.5 mh/kg" to keep in line with standard protocol guidelines.**

Changes in the text: **Page 4, Line 2 + Page 7, Line 19**

Table 2 (The Previous "Table 2" has now been changed to be "Table 1"

Comment 1: Why was methadone added during ketamine infusion, when the pain score was reported to be lower and doses of other opioids were reduced?

Reply 1**: The patient had been receiving Methadone before, during, and after the LDK infusion. We have included the specific dosages of Methadone that were used in Table 1.**

Changes in the text: **Legend of Table 1**

Comment 2: Why was the addition of methadone not mentioned above in the case presentation?

Reply 2: **To illustrate the overall amount of opioids that the patient was receiving, we use a standardized unit of MME (morphine milligram equivalents) when comparing the patient's opioid usage relative to the LDK infusion. We have included all specific opioids that the patient was receiving, including methadone, in Table 1.**

Changes in the text: **Table 1**

Comment 3 What conversion ratio was used for methadone : oral morphine?

Reply 3: **The conversation ratio used for methadone : oral morphine was as follows: If methadone 1-20, multiple number by 4; If methadone 21-40, multiple number by 8; If methadone 41-60, multiple number by 10; If methadone ≥ 61, multiple number by 12. We have included this conversation ratio, along with the conversion ratios for Hydromorphone (IV) Oxycodone (Oral), and Fentanyl (Transdermal Patch (mcg/ hr)), in the legend of Table 1.**

Changes in the text: **Legend of Table 1**

Reviewer B

Comment: There many series of ketamine administration, and this does not represent a new case, adding nothing to literature

Data is not new, and was largely reported in literature

Reply**: The paper describes the many challenges physicians and patients, consequently, face in the palliative care setting. One of these issues is the use of opioids and their numerous adverse effects. The patient under observation was deemed to have been on the maximum dosages of certain opioids and was under risk of acquiring opioid-induced hyper-analgesia. As a result, LDK infusions were deemed appropriate and potential benefits were clearly observed in this case. While ketamine is commonly used as a treatment for post-operative pain, protocols for using it to manage neoplastic and chronic pain and widely variable. Although it is used in many large academic medical centers, a consensus for a protocol for its use in neoplastic pain has yet to been established. This case report is specifically illustrating its novel use in a rural medical center were a ketamine protocol was specifically design for this selective case. Unfortunately, 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. While LDK (< 1 mg/kg) shows further potential to deliver excellent outcomes in pain management for cancer patient while simultaneously curbing the myriad of potential side effects of opioids through minimizing their usage, additional research is required to determine optimal dosing schedules, administration routes and the efficacy of LDK has the potential in palliative medicine.**

Changes in the text: **Page 6, Line 7 to Page 6, Line 19**

Reviewer C

Thank you for your interesting case report. I recommend some clarification, see below, and the following changes to be done:

Title: No comments

Abstract: See, comments below.

Keywords: No comments

Introduction:

Comment 1: First paragraph, line 15-19; the statement that: “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. This rapid increase in dosages in (is?) problematic due to the narrow therapeutic range of opioids and their high-risk side effects, such as respiratory depression.”

This statement must be modified, and new references must be added which supports these statements

Reply 1: The statement has been modified and we included citations for 2 review articles from Lancet Oncology and Pain Physician Journal to better support these statements.

Changes in the text: Page 2, Line 7 to Page 2, Line 10

Comment 2: In most clinical situation, opioids are usually well tolerated, with mild or moderate side-effects. What complication are you referring to? Please clarify.

Reply 2: We have included a list of opioid complications to better clarify what is being referenced.

Changes in the text: Page 2, Line 7 to Page 2, Line 10

Comment 3: Opioid tolerance could certainly be a problem. However, in cases were a 10-fold increase in opioid doses are necessary, opioids are seldom the right choice of drug and the problem is most often due to neuropathic pain and should be approached in a different way. Please clarify.

Reply 3: We address how the patient has been experiencing neuropathic pain and was given medications, such as Gabapentin, to address this.

Changes in the text: Page 3, Line 2 to Page 2, Line 6

Comment 4: There is not a high-risk of respiratory depression due to increasing doses/high doses, of opioids if the patient still experiences (severe) pain, but perhaps an increasing risk of

opioid-induced myoclonus and drowsiness. However, when an adjuvant drug is introduced (ex. Gabapentin, Pregabalin or NSAID´s) or a NMDA receptor antagonist as methadone or Ketamine and the pain starts to subside, then there is eventually a risk for respiratory depression, if not the opioid doses are monitored and reduced accordingly. Please clarify.

Reply 4: We included a list of side effects that can result from sole opioid usage. Additionally, we mention the close patient monitoring that was used and is needed when administering Ketamine for pain management.

Changes in the text: Page 3, Line 2 to Page 2, Line 6

Comment 5: First paragraph, line 20-22; the statement that: "The growing need of non-opioid analgesic treatment options, such as Low-Dose Ketamine (LDK) Infusion, for patients undergoing treatment for acute, chronic, and obstinate pain, calls for safer and more efficacious alternatives.", needs to be modified.

Reply 5: We have modified the statement to be clearer and illustrate a more direct point.

Changes in the text: Page 2, Line 10 to Page 2, Line 12

Comment 6: The use of Low-Dose Ketamine (LDK) Infusion could never be a cost-effective clinical alternative in the treatment of pain in a palliative setting, more than in very selected cases. However, the use of ketamine in different routes of administrations (PO as capsules or SC administration) could perhaps be a feasible and interesting alternative.

Reply 6: Cost-efficacy is a widely variable factor and thus we have removed it from our manuscript to avoid including misleading information. Additionally, we made sure to include the selective factors in our case that lead to making the clinical decision to use LDK: opioid side effects and tolerance with chronic use, patient declining the administration of larger and/or different opioid medications and increasing patient life expectancy. More specifically, our patient had specifically denied the administration of additional methadone because of how unbearable he found it to be. Additionally, despite being placed in palliative care, our patient had a longer than expected life expectancy and thus it was especially important to manage the patient's pain.

Changes in the text: Page 2, Line 10 to Page 2, Line 12

Comment 7: Why wasn´t methadone PO considered before a three-day IV infusion of Ketamine?

Reply 7: Methadone PO was also being given to the patient prior to undergoing the LDK

infusion. In order to make this information clearer, we have included a list of the medications that the patient was receiving on a daily basis in Table 1.

Changes in the text: Table 1

Comment 8: Second paragraph, line 23-25, the statement: "Here we report a case with Metastatic Prostate Cancer (Gleason 9 Adenocarcinoma), where LDK was used following an initial opioid-dependent pain management treatment to better manage pain and reduce complications from high-dose opioid use." What do you mean with an initial opioid-dependent pain management treatment? Please clarify?

Reply 8: The term "opioid-dependent" is certainly misleading; therefore, we have rephrased this sentence to read "opioid-based pain management treatment…"

Changes in the text: Page 2, 13 to Page 2, 15

Case description:

The 1st + 2nd paragraph, line 2-13, the report: "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 patient also had recurring issues with constipation, a likely side effect of the opioid medications he was taking. The patient was documented as a very friendly person who was in great spirits despite facing many adversities."

"The main criteria used to assess the patient was the Pain Assessment Scale, which was incorporated into the Physical Exam. The patient consistently reported a 9/10 on the Pain Scale as well as frequent bouts of constipation. An obvious diagnostic challenged faced during the study was due to the subjective nature of the Pain Assessment Scale. A "direct" measure of pain was not conducted and therefore, reliance on the patient's relative interpretation of his pain was the main determinant for the study".

Comment 9: It would be interesting to know the doses of Gabapentin and the different opioids also the efficacy of "as need" doses of opioids or other medications.

Reply 9: We have included a list of the medications that the patient was receiving on a daily basis in Table 1

Changes in the text: Table 1

Comment 10: Recurrent issues with constipation. The patient was given “Bisacodyl”, was Naloxegol never considered, in the treatment of a possible opioid-induced constipation issue, if constipation was a great concern?

Reply 10: Yes -- in fact the patient was put on a specific bowel regimen as a result for opioid-induced constipation. The bowel regimen included Senna 8.6 mg PO nightly, Miralax 17g POM daily, Bisacodyl suppository and tablet 10 mg, and Dexamethasone 6 mg PO daily.

Changes in the text: Page 3, Line 6 to Line 2, Line 10

Comment 11: The patient is described as: in great spirit despite consistently reporting 9/10 on the Pain Scale. It seems to me that the patient's pain not only explains the fact that he constantly reported 9 on the Pain Scale, and that this could perhaps be explained by other issues? The concept of “Total pain” could perhaps be worth mentioning here.

Reply 11: The patient’s consistent report of experiencing a 9/10 on the numerical rating scale points to the severity of the disease. The patient had metastatic prostate cancer which had spread to the pelvic bones causing immense pain. Prior to having the disease, the patient was a very active person, who enjoyed hiking and other sports. The patient’s demeanor had changed drastically since the progression of the disease and the only sign of positivity came after a few days of LDK infusion. A nurse’s note indicated that the patient was in “great spirits” following a dose of ketamine, displaying its potential success in being used as an adjuvant in the palliative care setting.

Changes in the text: Page 6, Line 7 to Page 6, Line 19

Comment 12: “A direct measure of pain was not conducted”: please clarify what you mean. The 3rd paragraph, line 14-19, the report:

Reply 12: This statement was originally purposed to mention the variable and subjective nature of assessing pain; however, we decided to remove this statement because the preceding sentence successfully addresses this limitation.

Changes in the text: Removed statement in question.

Comment 13: “The patient was receiving a daily Equianalgesic Dose [ED] of 82.71 mg Morphine PO (Table 2); however, was still reporting an average pain of 9/10 via the Pain

Assessment Scale. Clinical judgement for the patient was to not drastically increase the patient's opioid usage due to present adverse effects and pending inefficacy of additional opioids due to ascending drug tolerance. To avoid undesirable effects of high dosage of opioids, patient was considered for the LDK infusion." The opioid doses administrated to this patient, with a metastatic cancer in a palliative state, is low or must in any other way be considered as very moderate. With these doses of opioid, I can´t see how there could be a problem with ascending opioid drug tolerance. Please clarify.

Reply 13: The patient was receiving a high dose of opioids: 458.8 morphine milligram equivalents (MME) per day. While this information can be seen in Table 2, it is worth noting that the patient was receiving the following medications on a daily basis prior to the LDK infusion: Hydromorphone 5 mg IV, Methadone 30 mg PO, Oxycodone 60 mg PO, Fentanyl 12 mcg/hr patch.

Changes in the text: Table 1 + Page 3, Line 15

The 3 rd paragraph, line 19-25: "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 1). Under these guidelines, the standard concentration of the continuous infusion of Ketamine (Ketalar) was 100 mg in dextrose 5% 100 mL (1mg/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. (Table 2)"

Comment 14: Please add references supporting these guidelines of a "local LDK infusion".

Reply 14: We have all references that were used to design this pharmacological protocol of LDK infusion.

Changes in the text: Page 4, Line 5 to Page 4, Line 7

Additional comments:

Comment 15: I would appreciate more information about the patient´s pain: What do you as a clinician think about the cause and mechanism of the patient's pain? The effect of opioids used "as needed" on pain? Was the pain alleviated at rest? CT scan results: bone metastasis/bone compression as a sign of fractures?

Reply 15: 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's pain was consistent and was not alleviated at rest. The pain seemed to be both physical as well as emotional, due to the fact that the disease had spread to the boney structures as well as his depressed demeanor since he was first diagnosed with the disease.

Changes in the text: Page 6, Line 7 to Page 6, Line 19

Discussion:

General comments:

Comment 16: The discussion must be better nuanced and reflect the evidence and recommendations that exist today regarding the treatment of cancer-related pain. In cases of patients with a generalized cancer and thus with a limited life expectancy, opioid dependency issues is not a major concern, and should never be a cause to exclude opioid as the backbone in the pain treatment or to reduce doses per se out of such concerns. As you state, under-treatment for pain is a much greater concern in theses situation.

I would welcome a few sentences about methadone, an effective NMDA antagonist, and an establish treatment for neuropathic pain.

I would also welcome a discussion about the use of NSAID´s which could be a good adjuvant alternative in cases with bone metastasis? Perhaps, not in this case with a patient with a history of cardiovascular disease, but in similar cases.

Reply 16: Methadone was used in this case and provided only minimal relief to the patient. As far as NSAIDs are concerned, they are viable options, however, given the age of the patient in this case, NSAIDs were contraindicated due to the high likelihood of inducing acute renal failure.

Changes in the text: Page 3, Line 2 to Page 3, Line 10

Conclusion:

The line 25-27: "This case study suggests intravenous administration of LDK in cancer patient as a safe and effective analgesic to fill the growing need."

Comment 17: See comments above (Introduction): The use of Low-Dose Ketamine (LDK) IV Infusion does not seem to be cost-effective or safe (without an initial close monitoring of

patients with ongoing treatment with opioids) clinical alternative in the treatment of pain, more than in very selected cases.

Reply 17: We made sure to specifically state the importance of monitoring the patient when using LDK, and more specifically our include protocol, for pain management. Cost-efficacy is a widely variable factor and thus we have removed it from our manuscript to avoid including misleading information. Additionally, we made sure to include the selective factors in our case that lead to making the clinical decision to use LDK: opioid side effects and tolerance with chronic use, patient declining the administration of larger and/or different opioid medications and increasing patient life expectancy.

Changes in the text: Page 1, Line 9 to Page 1, Line 11

Comment 18: The statement is not justified by this case report or by the current base of evidence of Ketamine IV.

Reply 18: Ketamine has been established as reliable pain medication for alleviating post-operative pain. We agreed that cost-efficacy is a variable factor and have thus has removed it from our manuscript to avoid including misleading information. While the use of LDK for managing chronic neuropathic pain has not been established, we use this case report to illustrate how it can be used, with close initial patient monitoring, in selected patients were standardized pain management protocols are exhausted and/or unsatisfactory.

Changes in the text: Statement in question was removed + Page 1, Line 9 to Line 11

Comment 19: LDK IV infusion to alleviate post-operative pain is however an established treatment and is monitored accordingly.

Reply 19: We made sure to include the current guidelines and uses for ketamine in clinical