Palliative and Supportive Care

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Ketamine subcutaneous continuous infusion for depressive symptoms at home: A case report beyond pain use

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Case Report

Cite this article: Simões C, Julião M, Calaveiras P, Câmara P, Santos T (2024) Ketamine subcutaneous continuous infusion for depressive symptoms at home: A case report beyond pain use. *Palliative and Supportive Care* **22**(5), 1516–1520. https://doi.org/10.1017/S1478951524000798

Received: 11 March 2024
Revised: 11 March 2024
Accepted: 20 April 2024

Keywords:
Pain; depressive symptoms; ketamine; subcutaneous continuous infusion; home-based palliative care

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Abstract

Objectives. Ketamine has been widely used in refractory pain as an opioid adjuvant. Evidence suggests that ketamine can also have an essential role in easing depressive symptoms. Its rapid onset of action makes it a valuable choice in palliative care.

Methods. We present a case of a 70-year-old man with stage IV renal carcinoma and bone metastasis. The main symptoms included neuropathic pain, depression, and a persistent and severe desire for death.

Results. We started continuous subcutaneous infusion with morphine 30 mg and ketamine 100 mg/day. The dose of ketamine was incremented to the maximum of 250 mg/day. During the 28-day treatment, we observed an overall improvement in neuropathic pain, depressive symptoms, and other end-of-life psychological aspects of distress. Only minor psychological side effects were identified, which were controlled by using midazolam in the continuous subcutaneous infusion.

Significance of results. Some studies have already demonstrated the benefits of ketamine use in alleviating depression, using parental infusion or oral formulas, which are administered in hospice care. Our report enhances the benefit of the subcutaneous route for palliative patients cared for at home.

Introduction

Ketamine, a potent anesthetic, works by blocking *N*-methyl-D-aspartate receptors in the central nervous system, fostering rapid synaptic connections and promoting neural plasticity (Lossignol et al. 2005). Its potential as an anesthetic drug led to an increased use in pain medicine. Subanesthetic doses of ketamine are frequently employed alongside opioids to address neuropathic pain and enhance opioid analgesia (Kerr et al. 2011; Quibell et al. 2011; Vayne-Bossert et al. 2016). This approach is particularly beneficial for patients facing challenges in tolerating or responding to opioids. In such cases, the use of low doses of ketamine not only provides substantial pain relief but also enables patients to stay alert and responsive. As a result, ketamine emerges as a valuable choice for managing persistent pain and decreasing reliance on opioids (Pasero and McCaffery 2005). In palliative care, the subcutaneous delivery of medications and fluids becomes crucial when oral medication intake is not feasible for patients (Rodríguez-Campos et al. 2023).

In the realm of palliative care, where the focus is on enhancing the quality of life for individuals facing life-limiting illnesses, the management of depression poses a significant challenge. Traditional antidepressant treatments often fall short in providing timely relief. Recently, ketamine also gained attention for the treatment of depression (Fond et al. 2014; Stefanczyk-Sapieha et al. 2008; Thase and Connolly 2018), especially in the context of palliative care (Iglewicz et al. 2015; Irwin and Iglewicz 2010; Jancin 2012; Johnson 2018). While traditional antidepressants act on neurotransmitters, ketamine has a more direct and strong effect on the central nervous system. This novel approach has demonstrated preliminary efficacy in mitigating depressive symptoms, making it a promising drug for those grappling with the complexities of end-of-life care. One of its most notable applications in palliative care is its rapid onset of action and duration of effect (Fan et al. 2017), where time is of the essence, and alleviating psychological distress promptly is paramount. Moreover, ketamine's versatility allows for various administration routes, accommodating the diverse needs of patients within palliative care.

We present the case of a terminally ill person successfully treated for neuropathic pain, who also showed a decrease in depressive symptoms and several other psychological aspects of end-of-life distress, using continuous subcutaneous infusion of ketamine in a home setting.

Case description

We describe a case of a man in his 70s diagnosed with stage IV renal carcinoma, who undergone nephrectomy and had bone metastasis in the ribs and spine, leading to paraparesis and neuropathic pain in his lower limbs. Furthermore, he was experiencing intense pain (8 out of 10) caused by a large and deep pressure ulcer, according to the Edmonton Symptom Assessment Scale (ESAS). According to his family, the patient was experiencing intense pain and sadness, and it was evident that his physical pain connected to his existential suffering. He had asked, "Can you please tell me what kind of life is this?…" Accordingly to his family, he often openly expressed a subtle desire for death (DfD), engaging in deep introspection periods during the day while thinking about his fractured existence and personhood, while exhibiting episodes of crying. We conducted a thorough evaluation to check for depressive symptoms and psychosocial suffering using our admission and follow-up screening tools. Assessment for depressive symptoms using the single question for depression (SQD) (Julião et al. 2016) revealed positive. We used the DfD rating scale to assess the patient's DfD (Julião et al. 2013). Additionally, we evaluated the patient's burden and will to live (WtL), on a scale of 0–10 (0 = total WtL; 10 = worst possible WtL) (Julião et al. 2020). The patient's burden was positive, with the WtL score indicating 10. The DfD score was 4, indicating a persistent and severe desire to die. When inquired about his primary concerns, he raised issues about his pain. It became evident that his emotional and existential distress remained unspoken, likely due to the early stage of the team's engagement with him. The patient, a reserved and polite individual unaccustomed to sharing his feelings or emotional struggles, was still in the process of establishing a rapport with the health-care team during initial visits. After careful consideration and observation, the team decided to suspend the buprenorphine patch and switch to a continuous subcutaneous elastomeric infusion pump (SCEIP). The new treatment included morphine 30 mg and ketamine 100 mg/day. It is worth mentioning that the patient weighed 70 kg, and the ketamine dose of 2 mg/kg would count for 140 mg daily, but the a lower dose of ketamine was used to avoid any side effects and securely and closely monitor the treatment's effectiveness in reducing pain and improving the patient's mood.

Before the administration of ketamine, an assessment of the patient's vital signs, including blood pressure, heart rate, respiratory rate, and oxygen saturation, was conducted and verified to fall within the normal range. Subsequently, the family was comprehensively briefed on the potential side effects of ketamine, accompanied by information regarding alternative measures, both pharmacological and non-pharmacological. In anticipation of agitation or hallucinations, sublingual levomepromazine was prescribed on an as-needed basis.

After the patient was treated with SCEIP, the patient's pressure ulcer still caused localized neuropathic pain, but the pain was lower according to the ESAS assessment (4 out of 10). In the psychosocial assessment, the patient reported an "impressive improvement." All psychosocial items assessed were negative after 24 hours of subcutaneous continuous infusion. However, due to the maintenance of pain, the ketamine dosage was increased to 150 mg daily. The patient's caregivers observed some irritability and lack of attention, but no levomepromazine was given. It was suspected that the patient was experiencing a psychomimetic effect from ketamine, so 5 mg of midazolam was added to the perfusion. The patient started to experience a reduction in anorexia and asked for particular tasty and enjoyable foods in the following 48 hours while maintaining the same doses. No side effects were observed, and all psychological items were still negative (SQD: 0; burden: 0; DfD: 1; WtL: 0).

Following a fecaloid vomit, the patient was diagnosed with malignant bowel obstruction, and a 24-hour SCEIP with a combination of morphine 20 mg, metoclopramide 30 mg, butylscopolamine 60 mg, and ketamine 150 mg was started. Despite experiencing abdominal pain, nausea and vomiting, and a slightly increased anorexia, the patient remained calm, and in good spirits. His daughter was surprised to see that he could vomit during the day and continue to talk with her, sharing stories about his life and reading his magazines. To alleviate pain and increase appetite, the patient's ketamine dose was raised to 200 mg/day. This led to a swift improvement in both pain and appetite. However, within the first 12 hours of the new dose, the patient experienced some brief visual hallucinations. No medication was required to treat these hallucinations, and the patient's family members were able to help the patient cope with them until they subsided. If the family had any concerns or doubts, they were advised to contact the medical team. After maintaining the same doses in the continuous infusion for 6 days, the patient did not feel any depressive symptoms. He agreed to be cared for by his family and formal caregiver without feeling like a burden. He did not have any DfD and expressed a strong WtL. He informed the team that he felt "good and happy during those days." He requested that his daughter buy him the last volumes of the nature and wildlife magazines that he had yet to read. In the following days, slight anxiety was observed at nightfall when he would call his daughter, asking when she would arrive to be with him and his wife, who had an early dementia. The patient was experiencing end-of-day anxiety, which was not caused by the side effects of ketamine. The team decided to increase the dose of ketamine to 250 mg/day in the SCEIP due to increasing pain in his skin ulcer and sadness related to his wife's medical condition. This resulted in the patient's mood improving and the SQD becoming negative within 2 days. As the patient was stable in both physical and psychosocial symptoms, a 7-day SCEIP was initiated with morphine 140 mg, metoclopramide 210 mg, and ketamine 1400 mg. The SCEIP was maintained with the same doses until the patient passed away. No significant severe psychomimetic or hemodynamic adverse effects were observed during the 28-day period of subcutaneous ketamine administration.

Discussion

Our case underscores the potential of ketamine as a valuable tool in palliative care, offering a novel and effective approach to address both physical and psychological aspects of distress in individuals facing life-limiting illnesses, such as the DfD, burden, and fractured WtL. Additionally, to the best of our knowledge, our manuscript documents the uncommon use of ketamine in a home setting, administered via continuous subcutaneous infusion.

Considering our report and its follow-up, several noteworthy considerations emerge. First, physical pain is a prevalent symptom among palliative care patients, and ketamine has been studied for its analgesic properties in various types of pain, including neuropathic and opioid-resistant pain. Our report contributes to the existing literature on pain treatment, indicating that ketamine can

https://doi.org/10.1017/S1478951524000798 Published online by Cambridge University Press

be an effective and safe option, particularly for neuropathic pain. Our report demonstrates significant and sustained pain reduction from the beginning of treatment until the patient's death.

Another relevant aspect is the role of ketamine in reducing depressive symptoms. In palliative care, ketamine has been found to be a potentially effective treatment for depression (Fan et al. 2017; Iglewicz et al. 2015). It has been observed that the method of administration affects the effectiveness and onset of action of ketamine. Studies on parental ketamine consistently demonstrated a rapid onset, with effects appearing between 40 minutes and a few hours after administration (Thase and Connolly 2018). In a recent study using subcutaneous infusion of ketamine, a positive response has been seen in the first 6 hours of treatment in 50% of the patients (Lee et al. 2023). By using continuous infusion through the subcutaneous route, we observed a rapid improvement in the depressive symptoms, overall well-being and psychosocial issues, only roughly 24 hours after initiating the treatment.

Our case involved a man grappling with a severe advanced malignant disease, necessitating immediate relief due to the limited prognosis that precluded waiting for the delayed effects of traditional antidepressants. He faced significant depressive symptoms, a loss of interest in daily activities and life, and an intensified sense of burden due to escalating dependence. Administering ketamine through the subcutaneous route not only contributed to pain reduction but also proved effective in alleviating psychosocial suffering. This appears to be a more suitable option, given its quicker onset of action compared to traditional oral antidepressants, which may take 4–6 weeks to achieve efficacy (Goldman et al. 2019).

Previous studies indicate that the duration of ketamine's antidepressant effect may be influenced by the dosing schedule (Fan et al. 2017; Iglewicz et al. 2015; Irwin and Iglewicz 2010; McNulty and Hahn 2012). While 1-time doses may exhibit a significant reduction in effectiveness after a week of treatment, multiple daily dosing regimens have been suggested to have a longer-lasting impact (Goldman et al. 2019). In our study, we employed continuous ketamine administration using the SCEIP, resulting in a regimen akin to multiple daily doses.

Remarkably, our approach demonstrated a unique advantage, extending the antidepressant effect of ketamine for over 28 days until the patient's death, in line with another study (Irwin et al. 2013). This stark contrast to other daily-sustained dose regimens underscores the potential efficacy of continuous and slow infusion methods in achieving a prolonged posttreatment effect of ketamine. Our results led us to hypothesize that the sustained effect observed could be attributed to the continuous and gradual infusion approach.

During follow-up, we observed occasional fluctuations in the patient's mood, often linked to significant life events and concerns about his family. However, these fluctuations were temporary, and notably, the patient did not experience any clinically significant return of depressive symptoms. Even during minor mood variations, the patient demonstrated consistent emotional self-regulation and maintained insightful capacity over his feelings. Moreover, he not only regained but sustained the motivation to live a more purposeful life with his loved ones. This resilience and sustained motivation may indeed be linked to the continuous infusion of ketamine, presenting an intriguing aspect of its therapeutic impact.

Moreover, we posit that several factors might have contributed to the prolonged antidepressant effect observed in our case. A key consideration is our use of a higher dose of parenteral ketamine per kilogram of body weight at the initiation of the patient's treatment, surpassing the doses in comparable published studies (Lee et al. 2023; McNulty and Hahn 2012; Stefanczyk-Sapieha et al. 2008). This heightened dosage might have amplified the antidepressant effect of ketamine, potentially contributing to its prolonged duration.

In contrast to the rapid but short-term effects associated with intravenous administration, subcutaneous ketamine tends to exhibit a longer duration of action. This might suggest that subcutaneous ketamine may exert a more sustained antidepressant effect, allowing for a prolonged impact. Furthermore, the ability to adjust doses as needed during the evaluation period facilitated close monitoring of pain, emerging depressive symptoms, and other concerns, ensuring the treatment's effectiveness and tolerability.

Throughout the ketamine treatment, only a few side effects were observed, and these were effectively managed with low doses of midazolam administered in the SCEIP. Additionally, non-pharmacological measures, easily learned and implemented by caregivers, further contributed to side effect management, aligning with the same findings from a recently published paper from our group. To ascertain the long-term effects of stable subcutaneous ketamine doses, further research is warranted. This comprehensive approach not only emphasizes the need for continued investigation but also highlights the potential of subcutaneous ketamine as a well-tolerated and effective treatment option in palliative care.

It is essential to underscore some limitations in our report. First, we acknowledge the robust correlation between depression and pain. Consequently, we cannot dismiss the possibility that ketamine's effect may influence both facets of this connection. By alleviating physical pain, ketamine might also affect depression and the myriad factors contributing to a diminished sense of self-worth and a waning WtL, especially in the presence of severe physical symptoms and dependence of caregivers. We previously published a study (Julião et al. 2024) which also showed an improvement in the humor of a patient with central neuropathic pain undergoing ketamine treatment using SCEIP. While this observation does not inherently contradict the potential isolated effect of ketamine on depression, it underscores the need for future studies to concentrate on the use of ketamine solely for treating depressive symptoms, excluding physical symptoms such as pain. This approach aims to avoid the unintentional resolution of the combined symptoms of total pain.

Similar to the interconnectedness of pain and depression, a well-established link exists between depression and various psychosocial and existential features, as evaluated in our patient. These features encompass burden, DfD, and WtL. We posit that ketamine holds the potential to effectively alleviate these issues by mitigating total suffering and reducing its overall intensity. Despite these limitations, our findings emphasize the intricate nature of the relationship between pain and depression and prompt further exploration into targeted treatments for specific symptomatology to enhance the precision and efficacy of palliative care interventions.

While it might be advocated for the utilization of more comprehensive psychosocial assessment tools in palliative care settings, our approach diverged, opting for simpler screening tools aligned with our teams' follow-up procedures. Acknowledging the limitations inherent in our choice of simplified tools, we recognize that these constraints may impact the precision of our results. Furthermore, comparing our findings with studies utilizing standardized assessment methods may present challenges.

While parenteral ketamine offers faster antidepressant effects (Goldman et al. 2019), oral administration emerges as a potentially

https://doi.org/10.1017/S1478951524000798 Published online by Cambridge University Press

more suitable option for palliative care patients, particularly those in hospice or home-based care who favor noninvasive treatments (Iglewicz et al. 2015). Our report concentrated on the subcutaneous route, revealing promising results. However, it is important to note that our findings do not encompass data on the efficacy, safety, side effects, and acceptability of patients and their caregivers when utilizing alternative routes of ketamine administration. Nevertheless, the subcutaneous route demonstrates practical advantages, addressing potential delays in treatment associated with challenges in establishing intravenous access. This route can be administered by personnel with less specialized training, making it feasible in the home setting. As we explore the varied routes of ketamine administration, the focus on subcutaneous administration highlights its pragmatic application, emphasizing its accessibility, speed, and adaptability in the context of palliative care.

We acknowledge that our study employed a higher initial dose of ketamine compared to studies using parenteral and subcutaneous administration, potentially influencing the rapid and sustained effect observed in depressive and psychosocial relief. Notably, our use of subcutaneous ketamine introduces a variable absorption rate compared to intravenous or oral administrations, adding complexity to the interpretation of results.

The ability to adjust ketamine dosage in response to emerging pain or depressive symptoms could have played a pivotal role in enhancing its effectiveness. This adaptive approach may have contributed significantly to the observed improvement in depression. To comprehensively understand the long-term effects, further research is imperative, focusing on patients receiving stable subcutaneous ketamine doses.

In light of these considerations, our study highlights the importance of exploring initial dosage as well as further dosage adjustments and absorption variations in subcutaneous ketamine administration. This ongoing inquiry is essential for refining and optimizing the use of ketamine in palliative care, paving the way for more targeted and effective therapeutic interventions.

Ketamine therapy seems a promising drug helping ease depression and existential suffering in palliative patients and specially those wanting to receive care at home. Its adaptability and flexibility enhance its integration into the palliative care toolkit, accommodating varying medical conditions. To ensure safety and efficacy, a prepared team should be available daily to assess and follow-up on any potential psychomimetic and hemodynamic side effects.

Ketamine has the potential to reshape mental health care, especially in circumstances such as end-of-life care, providing hope for patients facing life-limiting illnesses and their families. However, further research is necessary to determine the best ways to administer ketamine, its long-term effects, safety profiles, optimal dosage strategies, and screening methods to identify which patients will benefit most from ketamine trials. This comprehensive approach underscores the need for continued exploration and refinement of ketamine's role in palliative care, offering support for patients and their families navigating the profound impact of life-limiting illnesses.

Acknowledgments. None.

Author contributions. CS and MJ were responsible for the initial draft's conception, design, and writing. PC, PC, and TS were responsible for the residents' assessments. CS and MJ gave overall input during the study and its writing. All coauthors made the revision of the final report and had full access to all the data.

Funding. This study received no specific grant from any funding agency, commercial or not-for-profit sectors.

Competing interests. None exist.

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