Case Report

Role of Intravenous Ketamine as Adjuvant to Opioids in Refractory Cancer Pain: Case Report

Yogesh Regmi[1], Ganga Sapkota[2], Bhawna Wagle[1]

[1]*Department of Anaesthesiology, B.P. Koirala Memorial Cancer Hospital, Bharatpur, Chitwan, Nepal*

[2] *GI and Breast Unit, Department of Surgical Oncology, B.P. Koirala Memorial Cancer Hospital, Bharatpur, Chitwan, Nepal*

ABSTRACT

Cancer pain is caused by continuous tissue injury, which may be due to surgery, infiltration of the surrounding organs including nerves, as well as from mucositis after chemo- or radiotherapy. The pain experienced by cancer patients needs a multimodal approach, including ketamine. Nerve involvement, chronic opioid therapy and continuous nociceptive input cause hyperalgesia. Chronic stimulation of the dorsal root neurons leads to hyperalgesia and resistance (tolerance) to μ opioid analgesics (hyperalgesia-tolerance). The NMDA receptor antagonist ketamine reverses tolerance to morphine. The management of cancer patient's pain with ketamine as an adjuvant to opioids is presented in case reports of two patients with cancer-related neuropathic pain, in which pain proved untreatable with the usual conventional pain therapies. Ketamine was administered IV route, in addition to morphine and the pain was controlled successfully in these patients. No side-effects were noted except drowsiness which responded to a reduction in the opioids dose.

Keywords: cancer, ketamine, NMDA antagonist, pain, refractory

Introduction

Cancer pain relief is the leading concern for the patients suffering from cancer and their physicians.[1] Cancer pain can develop from tumor invasion, musculoskeletal pain, visceral pain, radiation treatment effects, or neuropathy from chemotherapy. [2] No matter its source, uncontrolled pain can affect every aspect of a patient's quality of life, causing suffering, sleep disturbances, reduced physical and social activity, anorexia and mood disorder.[3] Statistics show that approximately 4.5 million patients die from cancer each year, and 3.5 million suffer from cancer pain daily. Despite of the fact, only a limited number of cancer patients are receiving adequate pain treatment.[2] Studies have shown that approximately 30–50% of all cancer patients experience pain, and out of them, 75–90% experience substantial life-altering cancer-induced pain.[1] Although cancer patients are surviving for significantly longer periods than in the past due to advancement in detection and treatment of cancer, however, the quality of life of these patients is frequently diminished and pain associated with cancer plays a main role in this decline of life quality.[3] Despite the side effects of opioids, most health care institutions uses opioids for cancer related pain particularly for moderate to severe pain. Cancer pain management is the most common problem in patients who have malignant tumor and the most feared illness for patients and their families.[4] Although cancer pain can be relieved in 80 to 90% of patients with WHO analgesic ladder approach, however in some pain syndromes there is an unfavorable response to conventional therapy.[5] Pain that is not readily responsive to opioids is often problematic and a challenge for physician.[6] Therefore, a comprehensive treatment plan is essential to control the pain especially in case of resistant pain. Sometimes invasive pain therapy is needed to manage cancer pain. The N-methyl-D-aspartate (NMDA)-receptor system has been shown to play an important role in these conditions.[7] According to the developing theory of neuroplasticity, "Agents that block the

Correspondence

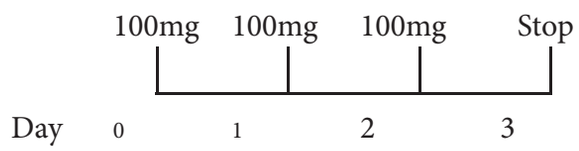
Dr Bhawna Wagle, *Department of Anaesthesiology, B.P. Koirala Memorial Cancer Hospital, Bharatpur, Chitwan, Nepal, email: bit2wagle@yahoo.com.*

activity of NMDA receptors may provide new tools for the treatment of opioid poorly responsive pain syndromes, particularly neuropathic ones".

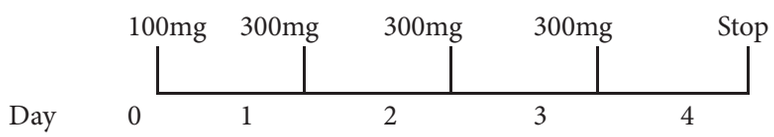
Ketamine is a NMDA receptors antagonist that modifies nociceptive pain pathways by acting in medial thalamic nuclei and dorsal horn of the spinal cord. Hyperactivity and overstimulation of NMDA receptors contribute to neuropathic pain. tolerance to opioids, hyperalgesia and allodynia.[8] Ketamine is licensed to be used as a general anesthetic; however, it is used beyond licensed for the treatment of neuropathic pain and hyperalgesia.[7] It is often used with the aim of reversing the state of tolerance and/or hyperalgesia associated with prolonged use of opioids rather than as a direct analgesic. Ketamine is considered as a third line drug and it provides an option for controlling unrelieved cancer pain and reduces the side effects of opioids.[9] According to several studies, opioid dosage can be reduced significantly while maintaining the same level analgesia by using ketamine as an adjuvant to therapy.[8]

'Burst' Ketamine Dose Escalation Protocol

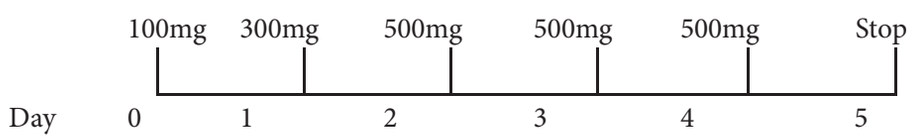
Starting dose 100mg per 24 hours via syringe driver If effective continue 3 days then cease



If 100mg ineffective after 24h hours, increase to 300mg If 300mg effective, continue three days then cease



If 300mg ineffective after 24 hours increase to 500mg



Cease ketamine at day 5 whether effective or not, earlier if ineffective and/or significant side effects.

Historically, the effects of intrathecal ketamine in reducing opioids such as morphine in cancer pain were evaluated by Yang et al.[10] Ketamine is commonly used as an analgesic in emergency medicine as an adjuvant drug in the perioperative setting. it is used for the induction and maintenance of general anesthesia, usually in combination with a sedative. Other uses include sedation in intensive care unit especially I emergency cases.[11]

Case 1

55 years old female with severe pain due to adenocarcinoma of the colon and bone metastasis with ascites and pleural effusion was admitted in ward. She was on sustained-release morphine, the dose of which was eventually increased to 1,200 mg total per day (over a 3-month period). The sustained-release morphine was supplemented with immediate-release morphine solution (600 mg) up to four times per day for breakthrough pain. Approximately 2 weeks before, she was gradually switched to fentanyl patches (Duragesic patch) with continued use of oral morphine solution for breakthrough pain. Patient wanted to stay at home with the family. Her local care team wanted home care service with round the clock nursing care for her. So she was shifted and switched to fentanyl patch presumably due to inadequate analgesia combined with increasing opioid side effects, especially constipation, itching and sedation. Over the week period, her pain continued to worsen, despite increasing numbers of fentanyl patches. At our initial evaluation, the patient had severe pain (verbal pain score 10/10) on 150 µg/hr fentanyl transdermal patches. Thus, the dose of fentanyl was immediately increased to 400 µg/hr. Despite of escalating dose of fentanyl patches to 600µg/hr and other supplemental therapies her pain remained uncontrolled. Her pain score was 9/10 on evaluation. The whole family was in distress. They wanted patient to be relieved from distress and excruciating pain. After evaluation IV,

ketamine infusion at 0.2 mg/kg/hr (192mg/24hr) was started on the first day with result of decrease in pain score 8/10, and then slowly titrated to 0.3-0.4 mg/kg/hr (300-450 mg/24hr) which gave her a good pain score 3/10 with a reduction in use of breakthrough medications. She was comfortable with good pain control on the same dose for four days and expired comfortably talking with the family members.

Case 2

A 40-year-old female with metastatic breast cancer involving bones, liver, lung, and pleura/chest wall with worsening back pain received weight-based intravenous (IV) ketamine for cancer-related neuropathic pain. She had responded poorly to outpatient pain regimen of morphine sustained and immediate release, gabapentin, and amytryptyline, with an initial pain score of 10/10.

Despite escalating doses of opioids and the addition of steroids, the patient's pain remained uncontrolled 4 days after admission. On 5th hospital day, utilizing a weight-based ketamine protocol, the patient was started on subanesthetic doses of ketamine at 0.2 mg/kg/h (288 mg/24 h) and titrated over 2 days to 0.4 mg/kg/h (576 mg/24 h). Then, on 3rd day when the patient's dose was increased to 0.4 mg/kg/h, adequate pain relief was charted within 120 minutes, "patient pain free and resting comfortably." Her pain continued to be well managed, with an average pain score of 5/10 with the ketamine continuous infusion with report of alteration in mood as side effects. On 6th day patient pain score was 2/10 and comfortable. Fentanyl patch (400 µg/hr) and oral medication continued thereafter, and patient died after three weeks. The use of weight-based dosing of IV continuous infusion was effective and tolerable in the management of opioid-refractory, neuropathic cancer pain.

Discussion

As in the two case reports ketamine worked effectively in patients who did not responded to opioids in combination with NSAID, amytryptyline and gabapentine. Ketamine is generally thought to be effective with good pain control and enabling a reduction in opioid doses. Dose of concomitant opioids can often be reduced and in some studies a dose reduction is advised as ketamine is initiated.[17] Several RCTs and systemic reviews have been identified looking at the efficacy of ketamine in cancer pain. The number of published studies, specially RCTs and clinical audits has risen steadily over the past few years. Some trials reported improvement in analgesia using ketamine as an adjuvant to opioids, whereas others failed to find any significant outcome. Cochrane Systemic Reviews from 2003 to 2011 suggested that ketamine as adjuvant to opioids for cancer pain is effective with good pain control and often enabling a reduction in opioids doses.18

The analgesia effects from ketamine at smaller doses may result from the action of different receptors sites than is caused by larger doses. Also, the wide dose range of oral ketamine reflects the variation in diagnoses among many study groups. Increased sensitivity to cancer pain ,which may be caused by damage to nociceptors or peripheral nerves following the acute administration of fentanyl can be prevented by pre-treatment with ketamine.[13] Eilers[14] reported a cancer case similar to the case 1 where severe tolerance to fentanyl was reversed by ketamine, their result suggested the early use of small dose ketamine may be reduce the tolerance of fentanyl. Ketamine may be used as a co-analgesic for breakthrough pain and for severe pain caused in end stage of cancer disease when invasive techniques are inappropriate or cause severe side effect. Regarding morphine consumption among cancer patients, two RCTs proved that use of ketamine in addition morphine decreased morphine use and reduced neuropathic pain intensity.[15] Ketamine is often used with the aim of reversing the state of tolerance and/or hyperalgesia associated with prolonged use of opioids rather than direct analgesics.[20] Many case reports suggest it is possible to reduce the opioid dose significantly while maintaining the same level of analgesia.[11] Some authors advise routine reduction in the opioid dose at the time of commencing ketamine treatment to minimize adverse effects such as sedation.[19] Hallucinations ,an unpleasant sensation such as empty head, and drowsiness were also reported. However, the side effects should be taken into consideration, especially when using a higher dose.[16]

Ketamine exerts a high incidence of psychotomimetic side effects (e.g. drowsiness, alterations in body image and mood, floating sensations, vivid dreams, hallucinations and delirium.[20] Consider starting with lower doses of ketamine and increase gradually as tolerated.[21] Consider reduction in concomitant opioid dose. As in case report 2, patient had alteration in mood benzodiazepines or haloperidol use minimizes the adverse effects. Use of benzodiazepines or haloperidol may only be necessary on a short temporary basis.[22]

CSCI of ketamine can cause significant irritation at the injection site. The use of ketamine can cause urinary tract symptoms e.g. frequency, urgency, urge incontinence, dysuria and hematuria. The causal agent has not been determined but direct irritation by

ketamine and/or its metabolites is a possibility.[23]

When pain does not respond to morphine it is considered problematic in cancer pain management like in the two case reports; ketamine, may be effective in improving opioid analgesia in pain syndromes among cancer patients, such as neuropathic pain; and reduced the pain intensity in the most cancer patients.

Conclusion

As in case reports, moderate to severe pain is not usually controlled by conventional pain therapies in cancer patients, had presumed neuropathic pain and had pain management compromised by opioids toxicity. In these patients, Ketamine was given as an adjuvant analgesic that resulted in good pain control. Hence, if conventional pain therapies either fail or are intolerable by the patient, alternative modalities should be considered. Ketamine can be used as an adjuvant analgesic for cancer pain treatment. There is a need for research to determine clear indication and benefit from adjuvant pain management therapy in cancer pain patients.

References

1. Murthy NS**,** Mathew A. Cancer epidemiology, prevention and control. Curr Sci. 2004; 86: 518–27.
2. Bhatnagar S. Interventional pain management: Need of the hour for cancer pain patients. Indian J Palliat Care 2009; 15: 93-4.
3. Wang XS, Cleeland CS, Mendoza TR, Engstrom MC, Liu S, Xu S, et al. The effects of pain severity on health-related quality of life: A study of Chinese cancer patients. Cancer. 1999; 86: 1848–55.
4. Alexopoulos EC, Koutsogiannou P, Moratis E, Mestousi A, Jelastopulu E (2011) Pain in cancer patients: the Greek experience. Eur J Oncol Nurs 15: 442-446.
5. Schug SA, Zech D, Dorr U. Cancer pain management according to WHO analgesic guidelines. J Pain Symp Manage 1990; 5: 27-32.
6. Singh DP. Quality of life in cancer patients receiving palliative care. Indian J Palliat Care. 2010; 16: 36–43.
7. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative review. Anesth Analg. 2004; 99(2): 482-85.
8. Blonk MI, Koder BG, van den Bemt PM, Huygen FJ. Use of oral ketamine in chronic pain management: a review. Eur J Pain 2010; 14(5): 466-472.
9. Hocking G, Cousins MJ (2003) Ketamine in chronic pain management: an evidence-based review. Anesth Analg 97: 1730-1739.
10. Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. Can J Anaesth 43: 379-383.
11. Peck TE, Hill SA, Williams M (2008) Pharmacology for anaesthesia and intensive care (3rdedn). Cambridge: Cambridge university press.
12. Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev 2017;6:CD003351.
13. Célèrier E, Rivat C, Jun Y, Laulin JP, Larcher A, et al. (2000) Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. Anesthesiology 92: 465-472.
14. Eilers H, Philip LA, Bickler PE, McKay WR, Schumacher MA (2001) The reversal of fentanyl-induced tolerance by administration of "small-dose" ketamine. Anesth Analg 93: 213-214.
15. Kotlicska-Lemieszek A, Luczak J (2004) Subanesthetic ketamine: an essential adjuvant for intractable cancer pain. J Pain Symptom Manage 28: 100-102.
16. Mercadante S, Arcuri E, Tirelli W, Casuccio A (2000) Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. J Pain Symptom Manage 20: 246-252.
17. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative review. Anesth Analg. 2004; 99(2): 482-85.
18. Blonk MI, Koder BG, van den Bemt PM, Huygen FJ. Use of oral ketamine in chronic pain management: a review. Eur J Pain 2010; 14(5): 466-472
19. Carr DB, Goudas LC, Denman WT, Brookoff

D, Staats PS, Brennen L et al. Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled cross-over study. Pain, 2004; 108(1-2): 17-27.

20. Fitzgibbon EJ, Viola R. Parenteral ketamine as an analgesic adjuvant for severe pain: development and retrospecti

21. Finkel JC, Pestieau SR, Quezado ZM. Ketamine as an adjuvant for the treatment of cancer pain in children and adolescents. J Pain, 2007; 8(6): 515-521.ve audit of a protocol for a palliative care unit. J Palliative Med, 2005; 8(1): 49-57.

22. Collins JJ, Grier HE, Kinney HC, Berde CB. Control of severe pain in terminal pediatric malignancy. J Pediatr 1995; 126(4):653-657

23. Dix P, Martindale S, Stoddart PA. Double-blind randomised placebo-controlled trial of the effect of Ketamine on postoperative morphine consumption in children following appendicectomy. Paediatr Anaesth 2003; 13(5): 422-426.