Editorial

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Is ketamine useful for pain management in patients with stage IV cancer?

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See "The effects of ketamine on pain control in stage IV cancer patients receiving palliative care" by Seonghoon Kim, Jihun Kang, Jongsoon Choi, Eunhee Kong.

Pain is a debilitating symptom of cancer, and its incidence is estimated to be greater than 90% in the advanced stage of the disease. According to the voluminous systematic review of 52 studies over 40 years, the pooled prevalence rate of cancer pain in all stages of disease was 53% (confidence interval [CI], 43%–63%), and those of cancer pain in advanced, metastatic, or terminal disease was 64% (CI, 58%–69%) [1]. More than one-third of cancer patients with pain revealed the pain intensity to be moderate or severe [1]. Therefore, several guidelines for the management of cancer pain have been published by the World Health Organization, National Comprehensive Cancer Network, American Society of Clinical Oncology, and European Society of Medical Oncology (ESMO). However, cancer pain remains an important subject for physicians in the clinical field.

Cancer pain has varied management depending on the severity of pain. Nonsteroidal anti-inflammatory drugs and paracetamol are generally recommended for the management of mild cancer pain, and opioids are the cornerstone of analgesic therapy for managing moderate to severe cancer pain. In addition, non-opioid analgesics such as ketamine and lidocaine have also been suggested as adjuncts for the management of patients with cancer pain [2].

Ketamine, a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, is a phencyclidine intravenous anesthetic used to induce and maintain general anesthesia due to its glutamate blocking effect. Interestingly, low (sub-anesthetic) doses of ketamine have analgesic effects and may suppress central sensitization, hyperalgesia, and opioid tolerance, which might be associated with neuropathic pain [2]. The reason for these effects is presumed to be that the ketamine may inhibit the activation of NMDA receptors in secondary afferent neurons, which is considered indispensable for enhancing pain sensitivity by repetitive nociception stimuli [3]. Unfortunately, there are only a few studies evaluating the use of ketamine as an adjuvant to opioids for the management of cancer pain, and the ESMO guidelines reported that there is a lack of evidence to support the routine use of ketamine in neuropathic cancer pain [4]. The effects of ketamine on pain control in patients with cancer are still controversial.

In this issue of *Kosin Medical Journal*, Kim et al. [5] investigated the effects of intravenous ketamine in patients with stage IV cancer with pain. A total of 253 patients were enrolled retrospectively, of which 112 patients received ketamine (ketamine group) and 141 patients did not receive

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ketamine (control group). The primary outcome identified a change in pain scores in both groups between the time of ketamine introduction and after 48 hours of introduction, and included proportions of a favorable response (pain score declined by ≥2), optimal response (pain score declined by ≥50%), and opioid-sparing effect (a reduction of opioid dose due to ketamine). The secondary outcome verified a decrease in visual analog scale (VAS), oral morphine equivalents (OME), inter-dose opioid frequency, and inter-dose opioid amounts in the ketamine and control groups at the time of ketamine administration, 24 hours, and 48 hours after administration. Based on the study results, the proportions of favorable response (odds ratio [OR], 3.84; 95% CI, 1.76–8.37) and optimal response (OR, 3.99; 95% CI, 1.73–9.22) in the ketamine group were higher than those in the control group. The degree of VAS score decreased more in the ketamine group than in the control group both at 24 hours and 48 hours after ketamine administration. In terms of adverse events, the ketamine group had a lower risk of depressive mood (OR, 0.31; 95% CI, 0.10–0.92) and a higher risk of delirium (OR, 2.06; 95% CI, 1.12–3.91) compared to the control group.

A recent retrospective study from Hong Kong showed that a favorable response rate to ketamine was 74.3% (n=52) in patients with cancer with refractory pain [6]. Another systematic review also reported that ketamine may be a feasible option for treatment of refractory cancer pain, despite data limitations [7]. However, a recent Cochrane review determined the effectiveness and adverse effects of ketamine as an adjuvant to opioids for refractory cancer pain in adult patients [8]. The Cochrane review included a total of three studies. Two studies showed that adding ketamine to morphine reduced pain severity and morphine requirements; however, one study that administered high-dose ketamine to opioids did not show any clinical benefit. Therefore, the review concluded that there was insufficient evidence to assess the effectiveness and adverse effects of ketamine as an adjuvant to opioids [8].

This study had several limitations. Firstly, the ketamine group consisted of patients with refractory cancer pain without adequate response to the administration of rapid-active morphine (20% of regular opioid dose) and increasing the dose of regular opioids (50%–100% increase of previous regular opioid dose); while the control group was defined as non-ketamine users. Therefore, selective bias cannot be ignored in this study design. Similarly, the initial VAS scores, OME, inter-dose opioid frequency, and inter-dose opioid amounts varied between the ketamine and control group. Second, since the initial VAS score of the control group was <3, it is estimated that it might be difficult to achieve a favorable or optimal response compared to the ketamine group with an initial score >3, which may have influenced the results. Finally, although this was a retrospective study, the effectiveness and adverse effects of ketamine could have been better identified if placebo was also administered in the ketamine group.

Nonetheless, to date, studies investigating the effectiveness of ketamine in the management of cancer pain are few in number, and few studies have been conducted among adult stage IV cancer patients with cancer pain. To our knowledge, this is the first study to determine the effectiveness of ketamine in the management of cancer pain in Korean patients with stage IV cancer receiving palliative care. Further large-scale prospective studies are required to understand the effectiveness and pathophysiology of ketamine for the management of cancer pain in patients with cancer with moderate to severe pain.

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Conflicts of interest

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