Perspective

Relevance of ketamine in the management of cancer pain

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Pain management in the context of progressive, far-advanced oncologic diseases continues to present new challenges for the treating physicians. The treatment goal of interventions in this patient population is to try to balance the analgesic effects with the adverse effects. The addition of adjuvant therapies to the armamentarium in pain management has allowed clinicians to treat pain in a multimodal approach incorporating medications with different mechanisms of action in order to improve its efficacy, thus minimizing side effects. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been utilized in the treatment of opioid-resistant pain syndromes of different etiologies and in the palliative care setting due to its opioid sparing effects at low subanesthetic doses (1,2). While at higher doses, it produces general anesthesia; at lower doses, it may inhibit the activation of NMDA receptors in secondary afferent neurons, which is thought to be essential for increased pain sensitivity (wind up) caused by repeated nociceptive stimulation (3).

Ketamine, like many opioid analgesics, has variable routes of administration including neuraxial, intravenous, subcutaneous, oral and topical, which makes it a versatile drug and is useful in this patient population. It's adverse affects are most commonly related to altered function of the central nervous system, including vivid dreams or nightmares, hallucinations and anxiety, as well as adverse gastrointestinal effects such as nausea, vomiting, loss of appetite, and abdominal pain (4,5).

Despite its wide use within the palliative care community, the benefits and risks of the addition of ketamine to an opioid regimen in this setting have not been well established. A recent Cochrane review evaluating the use of ketamine as adjuvant to opioids for cancer pain concluded that the current evidence is insufficient to assess effectiveness of this intervention (6). The manuscript by Hardy *et al*. (7) on subcutaneous ketamine in the management of cancer pain it is an attempt to add relevant information to increase the amount of evidence to support or reject the use of ketamine in this patient population. In this multicenter, dose-escalation, double-blind, randomized, placebo- controlled, phase III trial, Hardy *et al*. (7), studied the clinical benefit of a 5-day titration of subcutaneous ketamine versus placebo in patients with chronic cancer-related pain. The study included a heterogeneous patient population with chronic refractory pain due to life-limiting illnesses, multiple comorbidities, median survival of 2 months and baseline oral morphine of more than 300 mg/day. Although it constitutes a negative study in terms of the efficacy of ketamine as an adjunct to opioids and other co-analgesics, it is well designed study and deserves credit because of the known challenges posed by utilizing patients with far-advanced diseases as research subjects.

A limited amount of randomized controlled studies on the use of ketamine for cancer pain have been published in the literature. In 1996, a study conducted by Yang *et al*. (8) evaluated the effects of ketamine in intrathecal morphine analgesia for the treatment of cancer pain. When administered alone, the effective morphine dose was higher (0.38 mg/day) than in the morphine/ketamine group (0.17 mg/day). The average pain scores decreased from 7.95 to 1.95 with the addition of ketamine, demonstrating an enhancement in morphine's analgesic effect. Mercadante *et al*. (9) compared a subhypnotic bolus dose of intravenous ketamine (0.25 or 0.5 mg/kg) as adjuvant to morphine given to 10 cancer patients. Ketamine significantly reduced pain intensity in almost all the patients at both doses, phenomenon that was not observed with the placebo infusion. However, central adverse effects were also

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reported. These studies have been considered well designed with adequate power by the Cochrane review on ketamine for cancer pain (6).

Other small randomized studies have been reported in the literature. In 2007, a study conducted by Ishizuka *et al*. (10) evaluated the association of oral ketamine and morphine in the treatment of cancer pain. Thirty patients were randomized to a combination of oral morphine (10 mg, every 6 hours) and oral ketamine (10 mg, every 8 hours) or oral morphine (10 mg, every 6 hours) and placebo. Only 22 patients (9 in the ketamine group) completed the study. There was no statistical difference among both arms in terms of pain relief, number of times that the morphine needed to be adjusted, and side effects. In a more recent study, Salas *et al*. (11) included patients from several palliative care units with opioid-resistant cancer pain. A total of 20 patients (11 ketamine, 9 placebo) were randomized to receive ketamine or placebo with evaluation of pain intensity at different time periods up to 48 hours after baseline. There was no difference in pain intensity between the two groups due to worsening of symptoms during the study period. These studies as well as the study published by Hardy *et al*. (7), demonstrate once again the challenges faced by researchers while conducting research in patients with far- advanced diseases. From 185 patients randomized, only 42% (39/93) in the ketamine group and 38% (35/92) in the placebo group were able to complete the primary outcome of 5-day treatment. Twenty percent (19/93) of patients in the ketamine group experienced treatment failure after 24 hours at maximal dose (40.3% in placebo group) and therapy was discontinued in 18.3% (17/93) of patients due to toxicity.

Lauretti *et al*. (12) has also analyzed the role of oral ketamine as an adjuvant therapy for cancer pain randomizing 60 patients to a control arm (20 mg of oral morphine, 10 mg every 12 hours), nitroglycerin patch (5 mg/day), dipyrone group (500 mg, every 6 hours) or oral ketamine (0.5 mg/kg, every 12 hours). Even though the daily consumption of oral morphine on the control group was significantly higher when compared to the oral ketamine group, there was no statistical difference among the 4 groups in pain intensity. The patients were allowed to increase their oral morphine daily consumption as needed. In a subsequent study by the same group, 48 cancer patients were randomized to receive epidural morphine (control group), ketamine, neostigmine or midazolam (13). The association of low dose epidural ketamine or neostigmine to epidural morphine increased the duration of analgesia in this patient population. However, both of these studies have been considered to be methodologically flawed (6). As described above, evidence on the use of ketamine for the management of cancer pain is limited and somewhat conflicting. A negative study cannot establish the lack of efficacy, but the Hardy *et al*. (7) study was adequately powered and rigorously conducted, and strongly suggests that ketamine at the doses and administration protocol studied provides no meaningful analgesic benefit in a population with these characteristics. The study cannot address the possibility that a slower titration to a higher infusion dose may be beneficial in a subset of patients. The methodology credibly demonstrates no superiority of ketamine within the parameters of the study, but generalization of these results must be undertaken cautiously given the heterogeneity of populations with pain, the varied dosing strategies used, and the conflicting literature. For these results to have a significant impact and promote changes in our practice, they must be confirmed in further controlled trials.

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