

Ketamine: to be or not to be

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The attempt to support a clinical decision by an adequately powered randomized study is welcome, as palliative medicine needs to have clear information for providing guidelines and recommendations. The conclusion of this trial is that ketamine does not have a clinical benefit when added to opioid in cancer patients with a refractory pain condition (1).

Ketamine is a powerful NMDA-receptor-channel blocker available for clinical use, binding the phenylcyclidine site when the channels are in an open-activated state, and a second membrane associated site which decreases the frequency of channel opening. The NMDA-glutamate receptor is a calcium channel involved in the development of central sensitization of dorsal horn neurons. The channel is blocked by magnesium and is inactive in rest conditions. Prolonged excitation produces a change in the resting membrane potentials. As a consequence the channel unblocks and calcium moves into the cell resulting in a neuronal excitation. This effects seem to be mediated by the release of nitric oxide. The status of neuronal hyperexcitability is associated with hyperalgesia and allodynia, as well as a reduction in opioid responsiveness (2). Thus, an anti-NMDA-receptor agent is potentially useful in preventing or reversing states of hyperalgesia, even induced by opioids, when they lose analgesic effects and states of opioid-induced hyperexcitation prevail. Similarly, neuropathic pain conditions are commonly associated with states of excitation of spinal cord neurones (3). There is a good evidence from experimental animal models and small clinical studies in humans that ketamine relieves pain and reduce opioid tolerance in low doses. For these reasons ketamine has been used for years in the treatment of refractory cancer pain, not responding to opioids (4).

Few studies, however, afforded the problem to find some scientific evidence. A first attempt to analyse existing studies failed in finding consistent data (5). Only one study, based on a slow bolus of intravenous ketamine and assessing a short period of activity for three hours, reported data of the analgesic and adverse effects of systemic ketamine. In a randomized-controlled-double-blind, crossover double-dose study, ten patients with cancer pain unrelieved by morphine received a slow intravenous bolus of ketamine in doses of 0.25 mg/Kg, 0.50 mg/Kg or placebo. Ketamine, but not placebo, significantly reduced the pain intensity in almost all patients at both doses, with a more relevant effect on higher doses. Drowsiness was more marked with higher doses of ketamine, and other central effects were reported occasionally. This study short-term trial was encouraging although adverse effects were of concern, suggesting the need to individualize the treatment (6).

A small controlled study did not confirm the efficacy of ketamine in combination with opioids (7). Regardless the large inclusion criteria, that is patients with a pain intensity of ≥ 4 after 24 hours of an intravenous morphine infusion, of which doses are not reported, the sample size was quite low and doses of ketamine were within the minimal dose range, thus explaining the low adverse effects rate. However some patients were reporting a good analgesia, while others not, suggesting that selected patients may have major benefits.

Finally, in a well-powered study ketamine has been shown to do not have net clinical benefit when used as an adjunct to opioids and standard analgesics in cancer pain (1). It was based on the definition of refractory chronic pain (≥ 3 for pain intensity despite ongoing treatment with opioid and coanalgesics). Three dose levels of ketamine (or placebo), 100, 300, or 500 mg/day were provided according

to the clinical situation. The subcutaneous infusion of saline or ketamine was given in a 5-day schedule. Of allocated patients, only about 50% of patients received the treatment for 5 consecutive days, with discontinuation of the treatment due to clinical deterioration, treatment failure or adverse effects. Authors found a number needed to treat of 25 to get a positive outcome from ketamine, and patients on ketamine arm developed more adverse effects. CADSS score, which measures psychomimetic events, was increased in a consistent number of patients in both group and this can be a higher risk for patients who receive a potentially dissociative drug, regardless of the similar baseline values of placebo group.

The heterogeneity of patients is of concern. As described by authors and the high level of drop-out, participants were unwell. This is in contrast with the median performance status of 60, that is uncommon to observe in a population with a mean survival of 2 months.

Nevertheless, data are not surprising and it is expected that ketamine given to unselected population may produce poor advantages. According to the concept of the best existing evidence, efficacy of ketamine for chronic cancer pain is poor and burdened but central psychomimetic adverse effects. However, in situations where standard analgesic options have failed, ketamine could be a reasonable third line option. There are other areas to explore. For example the role of burst ketamine, given as a continuous infusion for two days at low doses (100 mg/day), may help patients with refractory pain conditions, eventually decreasing opioid requirement (8). With dose-titration protocol similar to that used in the randomized study of Hardy (1), 100, 300, and 500 mg/day, more than 50% of patients had relevant pain relief, which lasted over the drug discontinuation (9).

It is well known from anecdotal experience that less than 50% of patients are responsive to ketamine (10). Therefore any controlled study will be inferred by the number of patients who are non-responders. For example, enrichment studies could provide different results, particularly in a selected population of patients with complex pain situations. Randomized controlled studies are challenging in advanced cancer patients. Strict protocols often do not reflect the daily practice, where flexibility according to the clinical situation is the guide to provide the best solution for individual patients. Certain extreme and complex pain situations cannot be resolved by a level of evidence. When

a patient fails to respond to an initial analgesic treatment, several options are available, for example symptomatic treatment, the use of co-analgesics, opioid switching, change of the route of administration, all of these being not evidence-based. No randomized clinical trial may preclude the use of these modalities. A careful assessment and treatment by skilled people in selected environment allowing a strict monitoring, may provide the best option when randomized controlled studies fail to demonstrate any benefit for individuals.

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