

THE ROLE OF KETAMINE IN THE TREATMENT OF CHRONIC CANCER PAIN

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Abstract

Background and aim. Ketamine is a drug used for the induction and maintenance of general anesthesia, for the treatment of postoperative and posttraumatic acute pain, and more recently, for the reduction of postoperative opioid requirements. The main mechanism of action of ketamine is the antagonization of N-methyl-D-aspartate (NMDA) receptors that are associated with central sensitization. In the pathogenesis of chronic pain and particularly in neuropathic pain, an important role is played by the activation of NMDA receptors. Although ketamine is indicated and used for the treatment of chronic cancer pain as an adjuvant to opioids, there are few clinical studies that clearly demonstrate the effectiveness of ketamine in this type of pain.

The aim of this study is to analyze evidence-based clinical data on the effectiveness and safety of ketamine administration in the treatment of chronic neoplastic pain, and to summarize the evidence-based recommendations for the use of ketamine in the treatment of chronic cancer pain.

Method. We reviewed the literature from the electronic databases of MEDLINE, COCHRANE, PUBMED, MEDSCAPE (1998-2014), as well as chapters of specialized books (palliative care, pain management, anesthesia).

Results. A number of studies support the effectiveness of ketamine in the treatment of chronic cancer pain, one study does not evidence clear clinical benefits for the use of ketamine, and some studies included too few patients to be conclusive.

Conclusions. Ketamine represents an option for neoplastic pain that no longer responds to conventional opioid treatment, but this drug should be used with caution, and the development of potential side effects should be carefully monitored.

Keywords: ketamine, cancer pain, pain treatment, chronic cancer pain treatment, neuropathic pain

Introduction

Ketamine is a phencyclidine intravenous anesthetic used for the induction and maintenance of general anesthesia. In subanesthetic doses, ketamine has analgesic effects, so that it is used for the treatment of postoperative

and posttraumatic acute pain and for intensive care sedation or surgical and imaging procedures outside the operating room [1] Ketamine has also been reported to reduce pain intensity in patients with neuropathic pain of various etiologies: neoplastic [2,3], post herpetic neuralgia [4], complex regional pain syndrome (CRPS) [5], glossopharyngeal neuropathy [6], diabetic neuropathy [7,8], phantom limb pain [9] etc.

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In the management of chronic pain, ketamine administration can be oral, intranasal, sublingual, topical, parenteral (intravenous, subcutaneous, intramuscular, neuroaxial, intraarticular, intrarectal) [10]. In long-term treatment (for several month up to a maximum of more than one year), oral administration is preferred [11]. After oral administration, ketamine is metabolized in the liver by the cytochrome P450, having a bioavailability of 16%. Subsequently, norketamine is also metabolized in the liver and excreted through the kidney and bile [12,13,14].

The analgesic effect of ketamine in neuropathic pain mainly occurs through the antagonization of N-methyl-D-aspartate (NMDA) receptors and the activation of opioid receptors [15, 16].

NMDA receptors are inhibited by the binding of ketamine to one of their specific subunits. [14,16]. These receptors are involved in central sensitization, the development of hyperalgesia and allodynia in chronic pain, so these phenomena are reversed by the binding of ketamine to these receptors (antihyperalgesic effect) [16,17]. Its antiinflammatory effects may be also responsible for its antihyperalgesic effects [15,18].

Also, ketamine binds to all opioid receptors ($\mu > \kappa > \delta$) and the analgesic (antinociceptive) effects are only partially reversible by the administration of naloxone [19]. More recently, the role of ketamine in the activation of descending inhibitory pathways has been reported [20,21]. In the pathogenesis of pain, ketamine also acts by inhibiting the presynaptic neurons from the dorsal horns of the spinal cord through the release of excitatory substances such as glutamate and substance P [19].

Ketamine side effects usually occur with reduced incidence in the case of low doses used for analgesia [22,23]. The worst symptoms are central nervous system (CNS)-related: impairment of internal and external perception of reality, derealization, hallucinations, paranoid ideas, panic attacks, nightmares, vertigo, blurred vision, dizziness, memory deficits [23]. These side effects can be prevented by the concomitant administration of benzodiazepines in small dose. The gastrointestinal (nausea), liver (elevated liver enzymes), kidney (hematuria, dysuria) and cardiovascular side effects (tachycardia, systemic hypertension) are rarely described in palliative care settings [23, 24, and 25].

Using propoxyphene (analgesic drug used for mild and medium pain) together with ketamine may increase side effects such as dizziness, drowsiness, confusion, difficulty concentrating, and other nervous system or mental effects [26].

Knowing that NMDA receptor changes are partially responsible for the development of hyperexcitability, the role of ketamine in the treatment of cancer pain should be important. However, ketamine is recommended only as adjuvant analgesic for refractory cancer pain, for neuropathic pain and for pain that no longer responds to high doses of opioids or has predictable breakthrough pains

[27,28].

The aim of this study is to analyze evidence-based clinical data on the effectiveness and safety of ketamine administration in the treatment of chronic neoplastic pain, and to summarize the evidence-based recommendations for the use of ketamine in the treatment of chronic cancer pain.

Methodology

We reviewed the literature from the electronic databases of MEDLINE, COCHRANE, PUBMED, MEDSCAPE (1999-2015), as well as chapters of specialized books (palliative care, pain management, anesthesia and intensive care).

The keywords used for searches were: ketamine, cancer pain, cancer pain treatment, neuropathic pain.

The articles that met the following criteria were included:

The studies were performed on adults.

The studies were written in English.

Ketamine was administered in the treatment of chronic cancer pain.

The effectiveness of ketamine treatment was evaluated.

Results

The majority of the studies and papers found in literature analyze the efficiency of ketamine in chronic non-cancer pain setting and only a few of them assess the efficiency of ketamine in chronic cancer pain. This paper assesses and discusses the literature data available on this subject in order to summarize some important aspects that might reduce the pain of patients with malignant diseases.

In 1999, Lauretti et al. conducted one study which evaluated ketamine administration in chronic cancer pain. They investigated the role of oral ketamine and transdermal nitroglycerin as adjuvants of morphine for cancer pain. The study enrolled 60 patients and concluded that low-dose ketamine and transdermal nitroglycerin were effective coadjuvant analgesics. This study has weak power because of small number of patients [29].

In 2007, Ishizuka et al. performed a prospective, randomized, double blind study in 30 patients with the diagnosis of a malignancy with severe pain, comparing oral morphine and ketamine with oral morphine only for the treatment of chronic cancer pain.

They evaluated the intensity of pain, the presence of side effects, and analgesics prescribed at each appointment. The conclusion was that oral S (+) ketamine was not superior to placebo in the treatment of patients with oncologic pain when associated with morphine [30].

In 2009, Blonk et al. reviewed the literature regarding the role of oral ketamine in cancer pain. They appreciated that the evidences on the effect of oral ketamine in chronic pain was limited and quality of the studies is not very high. Their conclusion is that oral ketamine may have a limited

place as add-on therapy in complex chronic pain patients when other therapeutic options have failed [31].

In 2012, Chaudhary et al. conducted a cohort study, evidencing a decrease of neoplastic pain when ketamine was indicated as an analgesic adjuvant or in the case of ineffective opioid analgesia. The authors recommend the oral administration of ketamine, because it induces fewer side effects than intravenous or subcutaneous administration [32].

In 2007, Chung and Pharo evidenced the fact that intravenous ketamine administered in doses of 0.2-0.65 mg/kg/hour for 30 days, in a home care setting, decreased pain and reduced opioid requirements, without causing severe side effects [33].

One year later, Carter et al. shows the effectiveness of ketamine in palliative sedation without depressing cardiovascular and respiratory function [34].

Chazan S et al., in a small study on eight patients have concluded that ketamine is an efficient adjuvant analgesic for intractable severe pain, caused by metastasis, trauma, chronic ischemia, or central neuropathic pain [35].

In 2000, Mercadante et al. conducted a randomized, double blind, crossover study of 10 cancer patients with neuropathic cancer pain unrelieved by morphine, analyzing the impact of ketamine infusion added to morphine for the treatment of pain. They conclude that adding ketamine in infusion to morphine is associated with a significantly decrease in pain intensity [36].

In 2010, Schwartzman et al. performed a double-blind randomized controlled study, investigating the effect of intravenous ketamine in patients with malignant diseases and pain syndromes. All the participants received intravenously saline solution with or without ketamine for 4 hours daily for 10 days. The authors showed the beneficial effects of ketamine in reducing pain scores compared to placebo [37].

In 2012, Salas et al. performed a randomized, double-blind, placebo-controlled study, assessing the efficacy of continuous intravenous infusion of ketamine in patients suffering from cancer pain refractory to opiates, who had been admitted to palliative care units. The authors concluded that the study did not confirm the efficacy of the ketamine-morphine combination in refractory cancer pain, but they suggested that specific populations could be “good responders” for this therapeutic approach [38].

In 2004, Carr et al. conducted in a randomized, double-blind, placebo-controlled, crossover trial of 20 patients in order to evaluate the efficacy and safety of intranasal ketamine for breakthrough pain (BTP) in patients with chronic pain. They compared up to five doses of intranasal ketamine or placebo at the onset of a spontaneous BTP episode (pain intensity ≥ 5 on a 0-10 scale). Patients reported significantly lower BTP intensity following intranasal ketamine than after placebo ($P < 0.0001$), with pain relief within 10 min of dosing and lasting for up to

60 min. The results of this study suggest that intranasal administration of ketamine provides rapid, safe and effective relief for BTP but the number of the patients enrolled was too small to allow a clear recommendation [39].

In another study, Hugel et al. showed that intranasal administration of low S-isomer ketamine doses significantly reduced neuropathic pain [40].

In 2010, Jackson et al. conducted a randomized clinical trial in order to assess the effectiveness of subcutaneous ketamine. The authors administered ketamine subcutaneously, for 3-5 days, in escalating doses of 100, 300 and 500 mg/hour depending on the patient's requirements. They reported a 50% response rate, which lasted for two or more weeks, and 9% patients without pain [41].

Janet Hardy et al. carried out a multi-centric, dose-escalation, double-blind randomized, placebo-controlled clinical trial on 149 patients, assessing the effectiveness of subcutaneous ketamine versus placebo, added to opioids and coanalgesics, in the treatment of chronic uncontrolled cancer pain. The authors demonstrated a strong placebo effect and failed to show any additional clinic benefit for ketamine [42].

In 2014, Marchetti et al. analyzed, in a retrospective study on 55 cases of cancer and non-cancer chronic pain the efficiency of ketamine added to opioid treatment. They underlined that patients receiving opioid therapy tended to benefit from oral ketamine and showed few adverse effects. The conclusions of the study was that the longer patients receive an opioid, the more ketamine should be an option, with more likely analgesic efficacy and less likely secondary effects [43].

In 2012, Bell et al. conducted a second systematic review of randomized clinical trials, which evaluated ketamine administration in chronic cancer pain. The authors concluded that ketamine increased the effectiveness of morphine in the treatment of neoplastic pain and reduced morphine dependence, and they recommended the use of diazepam for the control of ketamine side effects (hallucinations) [44].

Two years later, Wick JY, in an online article evaluating the treatment of chronic cancer pain, stated that available data support the use of ketamine in the treatment of refractory cancer pain. Moreover, the addition of a low ketamine dose to patient-controlled morphine analgesia seemed to improve pain management [45].

In Palliative Care Guidelines of European Society for Medical Oncology (ESMO) which is a systematic review of the literature, the following recommendations are made regarding ketamine use:

1. The use of ketamine for the palliative treatment of neuropathic pain under the supervision of specialists.
2. The use of ketamine in complex neuropathic and vascular pain syndromes, where opioids have become ineffective.
3. Ketamine should be administered only after the

combination of opioids and oral adjuvant analgesics has become ineffective.

4. Ketamine is contraindicated in: intracranial hypertension, delirium, recent history of seizures, or psychosis [27].

Discussion

Despite the fact that ketamine has been used in different forms for cancer pain treatment for a long time, there are no good evidences and no clear recommendations for this. A limited amount of randomized controlled studies for the use of ketamine for cancer pain have been published in the literature. Most of the studies are small studies or case reports. Some of the studies show the benefit of using oral or parenteral ketamine for chronic cancer pain. On the contrary, some of these studies failed to show any benefit of using ketamine in this setting. More randomized clinical trials are required to evaluate all cancer types, as well as the beneficial and side effects of ketamine in the management of chronic neoplastic pain. The analgesic effect of low-dose ketamine probably occurs through its action on different receptors from those that act when the drug is administered in high doses [19,21,24]. Both for oral administration and for subcutaneous and intravenous administration, the doses described vary significantly from one patient to another, which is due to different diagnoses as well as to different groups of patients included in the studies.

Ketamine administration cannot be recommended as routine in patients with chronic neoplastic pain. As an analgesic, this drug has proved to be effective in patients with severe pain that no longer responds to conventional treatment. Oral ketamine can be beneficial in patients with intractable pain. In these patients, ketamine should be used with caution, when other therapeutic options have become ineffective. A good approach of these patients could be achieved by testing the responders and non-responders to the ketamine treatment and to continue the administration of ketamine only for the responders. Anyway, tests to determine response and non-response are not standardized. [45]. Until firm recommendations become available, doctors should weigh the potential risks and benefits for each patient.

Conclusion

Ketamine is a third line analgesic and represents an option for patients with uncontrolled cancer pain despite the optimal opioid and coanalgesic treatment. In these patients, ketamine reduces opioid requirements and decreases tolerance to some opioids.

The potential of ketamine as analgesic in cancer patients should be evaluated in future studies. Until then, ketamine should be used with caution, and the development of potential side effects should be carefully monitored.

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