MINI-REVIEW

Perioperative Intravenous Ketamine and its Usefulness for Chronic Pain Treatment

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ABSTRACT

Ketamine is a potent analgesic and dissociative anesthetic agent that has been used since its discovery and synthesis in 1962. The popularity of ketamine is due to its unique ability to produce rapid sedative, analgesic, and amnestic effects along with its beneficial secondary characteristics. The latter include bronchodilation and maintenance of both the reflexes of the airway and the tone of the sympathetic nervous system. Recent studies have also suggested previously unknown neuroprotective and anti-inflammatory properties. Due to its unique properties and versatility, ketamine has gained increasing popularity in pre-hospital and emergency medicine as well as is widely used by anesthesiologists and anesthetists around the world. Newer uses include low-dose analgesic protocols, adjuvant therapy in local anesthetic blocks, and indications in hyper-reactive airways as well as sedation for routine and complex procedures in operating rooms, emergency departments, and critical care units. Despite the potential advantages of ketamine, it has not proven to be universally popular due to its potentially unpleasant "psychotropic" effect, its potential as a drug of abuse, and the introduction of other sedative and analgesic drugs. This article will review the pharmacology and the different uses of ketamine in relation to acute and chronic pain management.

Key words: Acute pain, chronic pain, ketamine, N-methyl-D-aspartate antagonist, pain syndrome, post-operative analgesia

INTRODUCTION

Ketamine is one of the oldest medications used by anesthesiologists since it has been in clinical use for more than 50 years. In recent times, there has been a resurgence in the use of ketamine inside and outside the operating room as it has shown promise for the treatment of chronic pain, depression, and complex regional pain syndrome.[1] Perioperative, ketamine has become one of the first-line agents when patients do not respond to increasing doses of opioids or have contraindications for high doses, and regional anesthesia is not a chosen option, although evidence on how and when to use it has been kept in an ambiguous context. Ketamine has a multitude of pharmacological actions that include antagonism at the N-methyl-D-aspartate receptor, potentiation of central nervous system inhibition mediated by γ-aminobutyric acid, binding to μ, δ, and κ opioid receptors, as well increasing norepinephrine, dopamine, and serotonin levels, and interacting with cholinergic receptors, the purinergic system, calcium channels, and potassium channels. Finally, ketamine can block sodium channels as well as local anesthetics. Clinically, ketamine acts as an analgesic, dissociative, bronchodilator, anti-inflammatory, neuroprotective, and antidepressant anesthetic. Adverse effects are frequently observed at higher doses such as increased intraocular pressure, tachycardia, and awakening phenomena such as hallucinations, dreams, delirium, psychosis, severe confusion, nausea, vomiting, skin rash, or hyperglycemia, and only in the long-term psychological tolerance or dependence may appear. However, the application of low doses is generally well tolerated and, when used in combination with opioids, produces sparing effects thereof together with a reduction in the adverse effects related to these drugs. In the long term, ketamine can even help prevent chronic pain, although this concept is still under debate.[2]

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KETAMINE FOR ACUTE PAIN

The consensus guidelines on the use of intravenous ketamine (IV) for the management of acute pain developed by a panel of experts from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain and the American Society of Anesthesiology, hardly, they could be published at a more appropriate time like the current one.[3] The guidelines arise when we fight to implement multimodal analgesic regimes and, at least in the United States, to face a complex and unprecedented opioid crisis. How we have reached this difficult deadlock and why we fight against the use of opioids in pain management would be the main issues to assess and difficult to clarify in the first place. At first glance, one might think that the management of acute pain after surgery is simple, but nothing is further from reality. We know to a large extent which procedures are painful and we have tools to help identify patients who are likely to experience severe post-operative pain. However, despite the fact that we have a wide range of therapeutic modalities available throughout the world, acute post-operative pain remains undertreated due to a host of cultural, emotional, contextual, organizational, and logistical factors.[4]

The drafting committee of this review article on the use of ketamine in acute pain[3] has highlighted the deficiencies in the published research and the lack of more robust studies, specifically, the lack of available clinical trials to define their profile of efficacy/tolerability in surgical environments, and specific patient populations. Final recommendations have been based on answering six key questions:

- Question # 1: What patients and acute pain conditions should be considered for ketamine treatment?

In general, we conclude that subanesthetic infusions of ketamine should be considered for patients undergoing painful surgery (Grade B recommendation, moderate level of certainty). Ketamine can be considered for opioid-dependent patients or opioid-tolerant patients undergoing surgery (Grade B recommendation, low level of certainty). Because the evidence is limited to series of clinical cases, as well as to the clinical experience of the committee, ketamine can be considered for opioid-dependent patients or patients with opioids with pain related to sickle cell anemia (Grade C recommendation, low level of certainty). For patients with sleep apnea, ketamine can be considered as a complement to limit opioids (Grade C recommendation, low level of certainty).

- Question # 2: What dosage range is considered subanesthetic and how does the evidence support dosing in this range for acute pain?

We recommend that doses of ketamine in bolus should not exceed 0.35 mg/kg, and infusions for acute pain, in general, should not exceed 1 mg/kg per hour in environments without intensive monitoring, but we also recognize that the differences, between individual pharmacokinetics and pharmacodynamics, as well as other factors (prior exposure to ketamine), may warrant a dosage outside of this range. Adverse effects of ketamine will prevent some patients from tolerating higher doses in acute pain situations and, unlike therapy for chronic pain, lower doses may be necessary (0.1–0.5 mg/kg per hour) to achieve an adequate balance of analgesia and adverse effects (Grade C recommendation, moderate level of certainty).

- Question # 3: What is the evidence to support ketamine infusions as an adjunct to opioids and other analgesic therapies for perioperative analgesia?

In general, we conclude that there is moderate evidence supporting the use of subanesthetic bolus doses of ketamine IV (up to 0.35 mg/kg) and infusions (up to 1 mg/kg per hour) as opioid supplements for perioperative analgesia (Grade B recommendation, moderate level of certainty).

- Question # 4: What are the contraindications for ketamine infusions in the context of acute pain management and assess whether they differ from the configurations of chronic pain?

The evidence indicates that ketamine should be avoided in individuals with active pregnancy or psychosis (evidence of Grade B, moderate level of certainty) and poorly controlled cardiovascular disease (evidence of Grade C, moderate level of certainty). For liver dysfunction, the evidence supports that ketamine infusions should be avoided in people with severe disease (cirrhosis) and used with caution (with the approval of liver function tests before infusion and during the period between infusions with monitoring for elevations) in people with moderate disease (Grade C evidence, low level of certainty). The evidence indicates that ketamine should be avoided in individuals with elevated intracranial pressure and elevated intraocular pressure (Grade C evidence, low level of certainty).

- Question # 5: What is the evidence to support non-parenteral ketamine for acute pain management?

On the basis of a review of these studies, we conclude that the use of intranasal ketamine is beneficial for the treatment of acute pain, as it provides not only effective analgesia but also amnesia and sedation during the procedures. Particular scenarios in which to consider include individuals for whom IV access is difficult and children who undergo painful procedures (Grade C recommendation, low-to-moderate level of certainty). For oral ketamine, the evidence

is less robust, but small studies and anecdotal clinical cases suggest that it may provide a short-term benefit in some individuals with acute pain (Grade C recommendation, low level of certainty).

- Question # 6: Is there evidence to support analgesia with patient-controlled IV ketamine (IV-PCA) for acute pain?

In general, we conclude that the evidence is limited to the benefit of ketamine administered by IV-PCA as the only analgesic for acute or perioperative pain (Grade C recommendation, low level of certainty). We conclude, however, that moderate evidence supports the benefit of the addition of ketamine to an opioid-based IV-PCA regimen for the management of acute perioperative pain (Grade B recommendation, moderate level of certainty).

The dose and mode of the use of ketamine suggested in these guidelines differ from those used in recent PODCAST study, which used a single bolus of high doses of ketamine before incision in elderly patients and found a higher incidence of post-operative delirium without benefit in terms of pain.[5] In contrast, studies with a much smaller sample size where ketamine was added at low doses to post-operative opioids show only a small decrease in pain intensity but a substantial reduction of opioids and related adverse effects such as nausea and post-operative vomiting.[6] Look for ketamine dosage in Table 1.

KETAMINE FOR CHRONIC PAIN

In the past two decades, the use of intravenous ketamine infusions as a treatment for chronic pain has increased dramatically, with a wide variation in patient selection, dosing, and monitoring. This has led to an increase in calls from several sources for the development of consensus guidelines. In November 2016, the boards of directors of the American Society of Anesthesia and Pain Medicine and, shortly after, the American Academy of Pain Medicine approved the assignment to develop consensus guidelines. At the end of 2017, the entire document was sent to the Committees of the American Society of Anesthesiology and Pain Medicine and they studied the standards and practice parameters, after which additional modifications were made. The committee chair selected the members of the panel and both boards of directors based on their experience in the evaluation of clinical trials, research experience, and clinical experience in the development of protocols and the treatment of patients with ketamine. The committee developed the questions and the groups responsible for addressing each of them consisted of modules composed of 3–5 panel members in addition to the committee chair. Once a preliminary consensus was reached, sections were sent to the entire panel and new revisions were made. In addition to the consensus guidelines, an exhaustive narrative review was carried out.[1]

Consensus alignments were prepared for the following areas: Indications; contraindications; if there was evidence

Table 1: Recommended dosage of parenteral ketamine in clinical practice[1,3]

Route of administration	Regular dosage	Latency	Duration
Intravenous	1–4.5 mg/kg for the induction of general anesthesia 1–6 mg/kg per hour for maintenance of anesthesia 0.5–2 mg/kg in infusion for outpatients or 3–5 days with admission on alert for chronic pain (it is reasonable to start dosing with a single ambulatory infusion at a minimum dose of 80 mg that lasts at least 2 h and reevaluate before starting additional treatments) 0.2–0.75 mg/kg for analgesia of procedures, it can be repeated 0.1 mg/kg for the IV test dose; continuous infusion of 5–35 mg/h for acute or post-operative traumatic pain 1–7 mg/dose on demand mixed with opioids in analgesia controlled by patient IV-ACP	30 s	5–10 min after bolus
Intramuscular	2–4 times the IV dose; 5–10 mg/kg for surgical anesthesia 0.4–2 mg/kg for analgesia of procedures 0.10–0.5 mg/kg bolus dose for the treatment of chronic pain	2–5 min	30–75 min
Subcutaneous	0.10–0.6 mg/kg bolus for acute pain treatment 0.1–1.2 mg/kg per hour for chronic pain	10–30 min	45–120 min

of a dose–response relationship or a minimum or therapeutic dose range; if oral ketamine or another N-methyl D-aspartate receptor antagonist was a reasonable treatment option as an alternative to infusions; pre-infusion medical test requirements; configurations and personnel necessary to administer and monitor the treatment; the use of preventive and rescue medications to treat adverse effects; and what constitutes a positive response to treatment. The group was able to reach a consensus on all the questions.

The evidence supports the use of ketamine for chronic pain, but the level of evidence varies according to the condition and dose range. Most of the studies that evaluated the efficacy of ketamine were small and uncontrolled and were not double blind or were randomized inefficiently. Adverse effects were few and the rate of serious adverse events was similar to placebo in most studies, with higher doses and more frequent infusions associated with higher risks. The pathology group of complex regional pain syndrome (CRPS) was the most studied with an improvement between 4 and 12 weeks. As always, larger studies are needed to evaluate a wider variety of conditions to better quantify efficacy, improve patient selection, refine the range of therapeutic doses, determine the effectiveness of non-intravenous ketamine alternatives, and develop a greater understanding of the long-term risks of repeated treatments. In summary, for spinal cord injury pain, there is weak evidence supporting ketamine infusions (0.42 mg/kg per hour to 0.4 mg kg ranging from 17 minutes to 5 h for 7 consecutive days) for short-term improvements in pain (grade C recommendation, low level of certainty). For CRPS, there is moderate evidence supporting ketamine infusions (22 mg/h for 4 days or 0.35 mg kg per hour over 4 h daily for 10 days) to provide improvements in pain for up to 12 weeks (grade B recommendation, low to moderate level of certainty). For mixed neuropathic pain, phantom limb pain (PLP), postherpetic neuralgia (PHN), fibromyalgia, cancer pain, ischemic pain, migraine headache, and low-back pain, there was weak or no evidence supporting ketamine infusions for immediate improvements in pain (grade D, low level of certainty). Therefore, excluding CRPS, there was no evidence supporting ketamine infusions for intermediate or long-term improvements in pain.

CONCLUSIONS

Ketamine reappears as a useful tool in the field of perioperative pain medicine, and the risk-benefit ratio in low doses seems to be favorable in the majority of patients. Therefore, it can be a valuable strategy to help with various aspects of the current opioid crisis. Ketamine may have considerable value in reducing perioperative opioid doses and may reduce long-term use after surgery. There is currently no evidence to support this latter idea, and trials are urgently needed to assess whether the administration of low doses of ketamine or other opioid saving strategies has the potential to improve short-term outcomes and decrease the number of people that maintain the use or dependence of opioids in the long term. Regarding the current trend in the management of perioperative pain, ketamine has the potential to become a central pillar both to reduce our dependence on parenteral opioids and to accelerate the transition to a more widespread use of multimodal perioperative analgesia. Based on specific requests,we tried to provide recommended dosing ranges for chronic pain whenever possible. Although these recommendations are based on the existing literature, which is characterized by a lack of large, high-quality studies, one must recognize that the mechanisms of pain are strikingly similar for certain conditions (eg, deafferentation and cortical reorganization for PLP and spinal cord injury) and share considerable overlap even in widely disparate conditions (eg, central sensitization for fibromyalgia and neuropathic pain). Therefore, one could reasonably extrapolate ketamine dosing schemes for a condition that has been adequately investigated to another condition that has not been well researched, as is typically done for other analgesic medications.

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