



Medical Science

An International Journal

Ketamine: A Recent Review of Literature

Suraci, Nicholas^{1*}, Grandhi, K. Ravi²

1. MD, Northside Medical Center. 27. 500 Gypsy Lane. Youngstown, Ohio. 44504
2. MD, MBA. Northside Medical Center. 28. 500 Gypsy Lane. Youngstown, Ohio. 44504

*Corresponding author: Suraci Nicholas, MD, Northside Medical Center. 27. 500 Gypsy Lane. Youngstown, Ohio. 44504

Publication History

Received: 09 July 2016
Accepted: 3 August 2016
Published: 1 September 2016

Citation

Suraci Nicholas, Grandhi K Ravi. Ketamine: A Recent Review of Literature. *Medical Science*, 2016, 20(81), 186-191

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General Note

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ABSTRACT

Despite being on the market for longer than a half a century, Ketamine occupies a very unique space in the anesthesiologist's management preoperatively and for the management of pain. Over the past couple of decades, significant amount of research was conducted evaluating the mechanism of action specifically it's specific function within the central nervous system. Based on this increased understanding, ketamine is now being evaluated for use in a greater number of conditions including pediatrics, pain management, and depression. This article provides an overview of the history and some of the future uses of ketamine in various clinical settings.

Suraci, Nicholas and Grandhi, K. Ravi,
Ketamine: A Recent Review of Literature,
Medical Science, 2016, 20(81), 186-191,
www.discoveryjournals.com

Keywords: Ketamine, Nociception, Analgesia, Anesthesia

Abbreviations: NMDA, CRPS

1. INTRODUCTION

Ketamine was first described in the literature in 1965 and soon became FDA approved in 1970. Initially, the drug was used for its anesthetic effects, most commonly in pediatrics. Later, its analgesic properties increased its notoriety (Radvanky et al, 2015). Due to its side effect profile and potential for abuse, Ketamine is a schedule III drug and has fallen out of mainstream use. In recent literature, Ketamine has made resurgence for its potential benefits for anesthesia, pain disorders, depression, and potentially many other fields.

Ketamine has been used mainly to treat pain and to produce a dissociative state. Its analgesic mechanism is multifactorial and is in part due to its effects on the mu and kappa opioid receptors. The NMDA receptors participate in the development and maintenance of the development of pathologic pain after tissue injury: increased pain perception as a result of pain sensitization, in part from synaptic plasticity. Ketamine noncompetitively binds to the phenylcyclyline-binding site of NMDA receptors (Himmelseher and Durieux, 2005). Ketamine is a unique class of drug that induces a functional disorganization between the thalamocortical and limbic systems, which produce its dissociative state (Miller et al, 2011).

NMDA receptor:

N-Methyl-D-Aspartate receptor is a glutamate receptor found in nerve cells

2. CLINICAL APPLICATION

One of the most prominent issues within healthcare is pain. The NMDA receptor is noteworthy in anesthesia because of its role in pain sensitization. Blunting of this system has played an important role in the prevention and treatment of both postoperative and chronic pain. Neisters et al demonstrated in one study that ketamine was responsible for a decrease in connectivity in the brain regions responsible for pain sensing and affective processing. In chronic pain states, prolonged nociceptive stimulation causes activation and upregulation of the NMDA receptors resulting in amplified trafficking of pain signals to the brain. There is now ample evidence that NMDA receptor antagonism with ketamine is able to blunt this nociceptive input to the brain and decrease this sensitization (Neisters et al, 2014). Ketamine is particularly useful in pain syndromes that have a neuropathic component and cancer pain (Bredlau et al, 2014; Magneux et al, 2014). This evidence aids in shifting away from chronic opioid dependence. In contrast to opioids, the long-term efficacy of Ketamine is more controversial. Further long-term research is needed to confirm if this shift from opioids is appropriate.

Nociception:

The sensory nervous system response to certain stimuli

Ketamine's role in cancer pain can revolutionize treatment as ketamine appears to promote anti-inflammatory homeostasis and is immunomodulatory rather than immunosuppressive (De kock et al, 2013). In both animal and human models, ketamine prevents exacerbation and extension of the local inflammation without blunting the local process and delaying inflammatory resolution (De Kock et al, 2013). In contrast, opioids or derivatives of morphine can be immunosuppressive. In a review article by Grandhi et al, morphine's immunosuppressive and pro-inflammatory properties have the potential to cause micro-metastasis and angiogenesis leading to recurrence of the carcinoma.

Ketamine has a rapid onset and short half-life, which make it clinically useful for analgesia and anesthesia. It is a potent analgesic and has been used effectively for postsurgical situations requiring short, rapidly acting general anesthetic, post-operative short term analgesia, and procedural sedation, particularly in pediatrics and emergency medicine setting (Miller et al, 2011).

Intraoperatively, ketamine was noted to reduce opiate consumption in the 48-hour postoperative period in opiate dependent patients with chronic pain. Additionally, pain intensity decreased without an increase in harmful side effects (Loftus et al, 2010). This has a significant effect on the rest of patient management. When pain becomes severe, it can delay discharge, as well as result in poorer patient satisfaction (Radvanky et al, 2015).

In one recent study by Himmelseher and Durieux, postoperative surgical patients with morphine-resistant pain found that IV sub anesthetic ketamine combined with morphine-improved pain at smaller morphine doses than did morphine. To further support the use of ketamine, a 2011 review revealed a reduction in total opioid consumption and an increase in time to first analgesic request in

groups receiving ketamine. 78% of the ketamine treatment groups required less postoperative opioid analgesia and reported less postoperative pain (Radvanky et al, 2015). Not only is the administration of narcotics decreased, but also the time interval for medication is prolonged. A second review by Elia and Tramèr shows significant decreases in pain intensity at rest when ketamine is compared with a control at 6 h, 12 h, 24 h, and 48 hours postoperatively. All trials except one within the review report a significant decrease in morphine consumption when ketamine is used intraoperatively (Radvanky et al, 2015)

In addition to treating acute pain, ketamine may have a prominent role in preventing CRPS following surgery. Lubenow et al demonstrated that low dose IV ketamine in combination with an epidural had a significant reduction in not just acute pain, but it also eliminated chronic postsurgical pain up to one year later.

In addition to its use for pain, the use of Ketamine on the respiratory system is becoming more recognized. With the use of this agent, pharyngeal and laryngeal reflexes are only slightly impaired. Thus, the airway may be less at risk than is the case with other general anesthetic techniques. It is of particular value in children and poor-risk patients, and also in asthmatic patients, because it rarely induces bronchospasm (WHO, 1989).

3. ADVERSE EFFECTS

Common adverse effects include feelings of inebriation, nausea, psychotomimetic effects, perceptual disturbances and headaches with long-term use, possibly resulting in impaired cognition, memory, and mood. In addition, research shows that chronic use of ketamine may impair several memory systems including episodic and working memory (Radvanky et al, 2015). Also, it can cause hypersalivation, which is treated with atropine or glycopyrolate (Miller et al, 2011).

Although psychedelic side effects occur in a dose dependent fashion they already present themselves at relatively low doses, used in the treatment of chronic pain (20-30 mg/h). Both internal and external perception of reality are affected, causing auditory hallucinations, paranoid ideas, anxious feelings and inability to control thoughts, and derealization in time and space, visual hallucinations, increased external perception. Furthermore an intense sense of drug high is often perceived that some patients experience as extremely unpleasant, while others have an intense feeling of euphoria (Neisters et al, 2014). One team addressed these concerns and conducted a study using subanesthetic doses of ketamine. Results showed transient increases in the following psychiatric symptoms: positive and negative symptoms of schizophrenia, dissociative symptoms, and manic symptoms. Fortunately, these symptoms are only present at times of administration and usually disappear within sixty minutes of administration (Radvanky et al, 2015).

Approximately two-hundred cases of ketamine-induced uropathy have been reported in the literature, mostly in the context of chronic abuse, but five within medical analgesic use. Radvanky et al further investigated ketamine for addiction potential. Healthy subjects were given subanesthetic doses of ketamine for up to six months. Results showed no reports of cravings or abuse outside of the study, suggesting that ketamine in low doses is less likely to produce dependence.

4. PROSPECTIVE APPLICATION

What clinicians know of ketamine is constrained from limited use. The true potential of this drug is being brought to light, most notably in the realm of surgery. When preventing pathologic pain after surgery with ketamine, it is recommended that this medication needs to be applied throughout the entirety of the operation and into the postoperative period. This acts to decrease the nociceptive and inflammatory pathways in an attempt to reduce sensitization of the pain pathways. Rather than relying on anecdotal dosing schedules, developing an administration schedule is crucial in the management of pain (Himmelseher and Durieux, 2005).

Currently, the mainstay of surgical pain treatment has been with the administration of exogenous opioids such as morphine or fentanyl. The ever-increasing doses of opioids are clearly not without their side effects. Ketamine has been thrust into the limelight both as a standalone drug and as an adjuvant to other analgesics. It can counteract opioid-induced hyperalgesia, and prevent the development of opioid tolerance (Radvanky et al, 2015).

Most of the research conducted on Ketamine does not contain long-term data. However, Ketamine infusions have been reported to be safe and efficacious for the management of refractory complex regional pain syndrome (CRPS) in both the inpatient and outpatient setting. This therapeutic intervention can be especially helpful in the emergency room setting where large doses of narcotics are often injected to control pain. It has also been documented by Lubenow et al, that Ketamine booster infusions are likely to lead to fewer emergency room visits for these extremely difficult and serious cases of CRPS.

For those with chronic pain treated with long-term opioids, opioid-induced hyperalgesia is now becoming a big concern. Tolerance to opioids occurs quickly; as a result, nociceptive receptors increase. Consequently, pain perception increases and makes it difficult to treat and manage (Neisters et al 2014). Overprescribing narcotics is a glaring issue in healthcare. Ketamine can aid in changing this paradigm.

While ketamine holds a place in the prevention and treatment of postoperative pain, more large, high-quality controlled studies are necessary in order to determine which procedures it is best suited for and at what dosages and frequencies it should be administered (Radvanky et al, 2015).

Dysphoria:

A state of unease or generalized dissatisfaction

Due to dysphoric side effects associated with the dosage required to render general anesthesia, anesthesia providers may be reluctant to utilize this medication to its full potential (Goldfarb, 2014). However, for future studies, the evaluation of IV ketamine as an adjunct to general anesthesia appears to be a priority given the promising results, as minimal poor outcomes have been reported (Himmelseher and Durieux, 2005). Studies have demonstrated that ketamine infusion increases PaO₂

and decreased PaCO₂. During general anesthesia, patients treated with ketamine infusion show improved respiratory rate, increased oxygenation, and decreased hypercapnia (Miller et al, 2011). There is clear evidence that its use could be utilized further.

The effects of Ketamine on the respiratory system make it not only appealing for anesthesiology, but also on mechanically ventilated patients. Ketamine may be a safe and effective tool for maintenance sedation of mechanical ventilated patients. It decreases airway resistance, improves dynamic compliance of the lungs, and preserves FRC, minute ventilation and tidal volume, while retaining protective pharyngeal and laryngeal reflexes. It also does not promote respiratory depression (Miller et al, 2011)

Similarly, ketamine plays an important role in short-term sedation for pediatric patients who require simple procedures or short operative interventions. Ketamine allows patients to breath spontaneously. A 2013 study evaluated the role of ketamine and propofol (Ketofol) as it compared to ketamine and fentanyl. The combination of propofol and ketamine demonstrated several benefits because of hemodynamic stability, lack of respiratory depression, good recovery and potent post-procedural analgesia (Amornytin S, Siriraj, 2014). Ketofol was associated with decreased adverse events, decreased oxygen desaturation, and decreased nausea and vomiting. The reduced impact on breathing allowed for reduced positive pressure ventilation (Canvan 2013). Ketamine is currently being explored more extensively for use in pediatric patients for improved airway support.

In patients with refractory bronchospasm, Miller et al demonstrated that continuous infusion of IV ketamine decreases audible wheeze, bronchodilation requirements, and hypercarbia. Its tendency to preserve cardiac output and relax bronchial smooth muscles has made this an attractive option for induction and maintenance of general anesthesia, especially those with reactive airway disease.

In addition to its clinical significance in the fields stated earlier, Ketamine also demonstrated its use in the realm of Psychiatry and management of other chronic conditions.

Major Depressive Disorder (MDD) is a debilitating condition that affects close to 6.7% or 15 million Americans according to the National Institute of Mental Health, which is only increasing steadily (Health, 2014). Although there is a number of anti-depressants on the market, there is a need for better treatments especially in situations of treatment resistance or depression with homicidal or suicidal ideation. The majority of these anti-depressants work through monoaminergic mechanisms, which is based on the theory that depression occurs because there is an imbalance of neurotransmitters such as serotonin, dopamine, and/or norepinephrine (Ladarola et al, 2015). However, there is increasing evidence that there might be other neurotransmitters that play a role in depression, in particular, the hippocampal prefrontal circuit (HC-PFC), which often has decreased functional activity in depression (Muller et al, 2016). Of particular interest is that, the HC-PFC uses N-methyl-D-aspartate (NMDA) receptors and gamma-aminobutyric acid type A (GABA_A) receptors (Thierry et al, 2000). Ketamine interacts with both these receptors. Ladarola et al and Naughton et al found that Ketamine has a rapid and potent anti-depressant affect. Based on these findings, over 50 clinical trials have been registered on clinicaltrials.gov (Muller et al, 2016).

A number of recent studies have shown that Ketamine may play an important role in managing the symptoms associated with major depression and bipolar disorders. One of the first trials was performed at Yale University in 2000, with a cohort of 7 patients, which showed significant improvement in depressive symptoms within 72 hours of starting ketamine. Since this initial success, many more trials have been performed which have shown similar success. Of particular interest in the last few years has been its impact in patients who maybe acutely suicidal. Reductions in suicidality can happen as quickly as 40 minutes after the start of infusion in some of these patients, which is in contrast to other anti-depressants which can take days to weeks to function (Price et al, 2014). However, on average ketamine on average lasts about 7 days. It's short-term adaptability and potential use offers a solution to a serious

problem, with very minimal side effects (Muller et al, 2016). Although the thoughts of Ketamine as a solution have been around since 2000, its potential role has really taken off in the last couple of years. The majority of the initial work on ketamine for depressive episodes has been extremely positive. As a result, a greater number and larger research trials have to be performed, with a special focus on developing quantifiable benefits.

PTSD is another condition with not only an unknown pathophysiology, but also no good treatment option especially in those cases that are especially severe. As a result, ketamine, which is one of the most well-known drugs for its dissociative properties, has been tried for treatment. One retrospective study by Schoneberg et al found that there were increased symptoms of acute stress disorder (including symptoms of dissociation, re-experiencing, avoidance, and hyperarousal). However, another study by McGhee et al found that in a retrospective study at military hospital, patients who received ketamine had lower rates of PTSD than those didn't despite more severe burns, greater burn size, longer stays in the Intensive Care Unit, and more surgeries. The positive efficacy might be due to the fact that ketamine is able to disrupt the memory process, which can be either the hospital experience or the trauma process itself. However, more research is necessary to clarify the exact risks and benefits. Future expansion of the role of ketamine should look at its impact on other causes of PTSD.

Fibromyalgia is one of the most complicated diseases to understand, with multiple potential different mechanisms of action. There is truly no underlying pathology regarding the pain. In fibromyalgia, there is a reduced central nervous system sensitization, which leads to associated increased pain. NMDA receptor inhibitors such as a ketamine reduce the activity of glutamate, which is the main excitatory neurotransmitter in the brain. However, the more intriguing part of ketamine is that it may also enhance circulator functioning volume, which may optimize states of low blood volumes or other circulatory defects. In 2011, Noppers et al found that ketamine infusions reduced pain levels in fibromyalgia by 50%, however the study was extremely short lived, last less than 2 hours. In 2007, Guedj et al found that ketamine increases blood flow to the parts of the brain associated with pain regulation in fibromyalgia patients. If ketamine was not able to increase the blood flow to parts of the brain associated with fibromyalgia (medial frontal gyrus) then there was insufficient improvement in pain (Gued et al, 2007) While both of these theories have gained some traction and are being studied in animal models, another theory surfaced regarding the potential role of dopamine, which is why SSRIs often play a key role in management (Wood, 2000). More research needs to not only been done on the impact of ketamine on fibromyalgia, but also the underlying etiology of fibromyalgia.

5. CONCLUSION

Still, although ketamine treatment is linked to a variety of side effects mentioned earlier. It is the impression of the treating physicians that the benefits outweigh the risks in specific patient populations. In order to substantiate these impressions, additional placebo or active-comparator controlled studies are required that indeed show can demonstrate its potentially useful effects in the numerous fields of healthcare.

SUMMARY OF RESEARCH

This report aims to support the literature for Ketamine and its potential use.

DISCLOSURE STATEMENT

There is no special financial support for this case report from any funding agency or conflicts of interest.

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