REVIEW ARTICLE

Bali Journal of Anesthesiology (*BJOA*) 2019, Volume 3, Number 1: 74-77
E-ISSN: 2549-2276

Published by DiscoverSys

Ketamine: old drug, a new option

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INTRODUCTION

The search of the ideal anesthetic agents started way back in the year 1957 when Woodbridge mentioned such criteria: motoric, sensory, autonomic as well as cognitive block. In 1950s Parke-Davis pharmaceutical company developed cyclohexylamines. Sernyl was the first agent to undergo clinical study; it was known as phencyclidine (PCP). Many studies, however, mentioned severe psychotomimetic effects of this drug in the study population. In the following era, 2(O-Chlorophenyl)-2-methylamino cyclohexanone or CI-581, identified as ketamine, was produced as the PCP derivative. Animal studies showed better results with this agent which generated anesthesia and analgesia effect similar to PCP with fewer side effects.[1,2]

Unique properties and recent development in the areas of clinical properties of ketamine make this agent popular for a long time. This anesthetic agent has a wide range of indications. Many areas of clinical application of ketamine are explored in many studies. However, not many clinicians are familiar with the wide range of clinical applications of ketamine.

Ketamine affects the central nervous system (CNS) to cause dose-dependent depression, which leads to a dissociative state, described as analgesia and amnesia without profound loss of consciousness. The patients receiving ketamine seem to be unaware of the environment. The recovery time is dose-dependent and emergence is often accompanied by psychotomimetic reactions (hallucinations, vivid dreams).[3]

Ketamine has additional effects on the respiratory system, which includes bronchodilation, minimal respiratory depression with only mild hypercapnia, and preserved protective airway reflexes. These effects are generally beneficial in comparison with other anesthetic agents. In the cardiovascular system, ketamine increases heart rate and blood pressure as well as increases pulmonary artery pressure, especially in patients with preexisting heart disease. These may happen due to sympathetic stimulation, which creates a direct effect on the heart.[3]

Ketamine consists of two optical enantiomers, R(-) and S(+), and the preservative benzethonium chloride. It has a relatively short distribution and elimination half-lives with a-elimination phase lasting a few minutes and the p-elimination half-life lasting 2-3 hours.[4] The contraindications of ketamine are uncontrolled arterial hypertension or hypersensitivity to the drug.[3] Studies mentioned ketamine should be used with caution in patients with right heart failure and coronary artery disease.

MECHANISM OF ACTION

The effect of ketamine in CNS is a complex interaction of multiple binding sites, including N-methyl-D aspartate (NMDA) and non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic, and monoaminergic and opioid receptors. Additionally, studies also mention the interaction with Na and L-type Ca channels. When Na channels are inhibited, this leads to a local anesthetic effect; where the blockage of Ca channel leads to cerebral vasodilation. The clinical properties of ketamine happen due to such interactions. The antagonistic effect of the NMDA receptor is responsible for amnestic, psychotomimetic, analgesic, and neuroprotective effects of ketamine.[3,4]

The NMDA receptor is classified as an ionotropic receptor, which is activated by glutamate, commonly found neurotransmitter in the NS. This ligand-gated ion channel is permeable to calcium, sodium, and potassium. The NMDA receptor requires glycine as its co-agonist and is hindered by magnesium. The NMDA receptor involves in the development of the pain pathway in chronic pain cases. Ketamine decreased stimulation in the CNS through the NMDA receptor. In the NMDA channel, phencyclidine receptor binds to ketamine and this inhibits activation of glutamate. However, the binding site of phencyclidine has some similarities with a binding site for magnesium.[4]

In several cases, non-NMDA glutamate receptors may be activated by agonist quisqualate (AMPA) or kainate. In the past, these receptors were thought not to interact with ketamine. However, recent animal studies showed the contrary. This effect is facilitated through glutamate/NO/cGMP system. Non-NMDA receptor activation also stimulates NO synthesis so that this will increase the production of intracellular cGMP. NO is well-known as its role as a peripheral and central neurotransmitter and pain reception. This may explain some of the ketamine profiles which were not explained by NMDA interaction.[4]

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KETAMINE AND POSTOPERATIVE PAIN

Postoperative pain remains as one of many undesirable complications for patients undergoing surgery. Many studies focus on the prevention and management of postoperative pain. Delay of treatment may lead to poor outcomes. The analgesic effect of ketamine brings up the idea to utilize ketamine as an adjuvant to perioperative analgesia. Intravenous ketamine is proven to decrease postoperative pain up to 48 hours.[5] Study showed that decreased pain intensity within the first 6 hours and this difference was statistically significant up to 48 hours postoperative. The study also showed intravenous ketamine decreased 24 hours morphine consumption and delayed the first rescue dose.[6]

In daily practice, both decreased pain intensity and opioid requirement are associated with a good analgesic profile. One study showed the average morphine consumption after major surgery was around 40 mg. The average morphine consumption and the intensity of postoperative pain were reduced after the administration of intravenous ketamine.[6] Therefore, decreased pain intensity after ketamine administration is linked with the opioid-sparing effect.

Even though morphine consumption was decreased after ketamine administration, the incidence of morphine-related adverse effects did not change. This might happen because these studies did not evaluate the adverse effects specifically. Additionally, the decrease of morphine consumption was not clinically significant to reduce the adverse effects.[6]

Another study mentioned that ketamine was able to delay the administration of the first rescue dose. This result was statistically significant, but it was not significant clinically.[7] However, this supported the efficacy of ketamine as an analgesic agent. The long-term effect of ketamine postoperatively was revealed in one study, which mentioned the beneficial effect of ketamine for persistent pain around the surgical site up to 6 months postoperatively. This phenomenon was explained by the antagonist effect of ketamine at the NMDA receptor.[7]

The role of ketamine exerts its role to modulate postoperative pain, both as standalone agent and as an adjuvant to other analgesics, such as fentanyl or morphine. The administration of caudal ketamine in pediatric patients was mentioned in some studies. The clinical trials concluded that ketamine might be used for caudal analgesia.[6,7]

The important component to be discussed when administrating ketamine as a perioperative analgesic agent is harm. The risk of adverse effects, such as hallucinations, is the main reason why ketamine is unfavorable for some clinicians. Studies mentioned that consciousness of the patient and the use of benzodiazepines affected the risk of hallucinations after ketamine administration.[8] However, benzodiazepines are not protective of hallucination. The study showed even after the administration of benzodiazepine premedication, some patients still suffered from hallucination following ketamine administration. Patients receiving ketamine should be informed with the side effects and must be monitored closely.

KETAMINE AND PREEMPTIVE ANALGESIA

The analgesic profile of ketamine is profound even in small doses. This is beneficial to supplement local or regional anesthesia. Some studies mentioned that the administration of ketamine before any noxious stimuli is even more effective. This is known as preemptive analgesia. The purpose of preemptive analgesia is to diminish the development of pain pathway in the CNS. In the long term, this aims to reduce the postoperative analgesic requirements.[9]

After the afferent nociceptive impulses arrive at the spinal cord, the CNS sensitization occurs. The receptor responsible for pain memory is the NMDA receptors. Therefore, NMDA antagonists may diminish the induction of central sensitization and eradicate hypersensitivity. This leads to the prevention of pain. Currently, ketamine is the only NMDA antagonists approved by the Food and Drug Administration. Many studies have successfully established the efficacy of small dose ketamine as preemptive analgesia. Small doses of ketamine administered preemptively was shown to decrease opioid requirement in the postoperative period.[8] In patients scheduled for cholelithiasis surgery who received ketamine 0.25 mg/kg IV preemptively, postoperative analgesic requirements decreased. Another study mentioned that administration of ketamine 0.5 mg/kg bolus before incision generated better pain control in comparison to those who received ketamine after wound closure.[10]

Though timing and dosing differ between one study to another, overall administration of preemptive ketamine decreases opioid use postoperatively. In average, opioid consumption was decreased up to 60% in comparison to those who did not receive ketamine. This was related to a lower incidence of opioid side effects.

KETAMINE AND NEUROSURGERY

In the past ketamine was highly avoided in patients with increased intracranial pressure (ICP). However, recent studies discovered the neuroprotective role of ketamine. Racemic ketamine will

increase ICP, especially when the ICP is already increased and the IV dose of ketamine is more than 1 mg/kg. This happens because increased arterial PCO2 because of ketamine-induced ventilator depression. Additionally, increased cerebral blood volume caused by increased arterial pressure also leads to increased ICP. However, the latest study showed 0.5-5 mg/kg ketamine did not increase ICP when ventilation was controlled (normocapnia).[11] Mild hyperventilation and benzodiazepines might contribute to ICP increase following ketamine administration. A study in patients with head injury showed there was no increase in ICP following ketamine administration when controlled ventilation and adequate sedation were used.[12]

Animal studies revealed increased cerebral blood flow (CBF) after administration of racemic ketamine and cerebral vasodilator N2O while decreased CBF was found after ketamine and barbiturates administration.[13] This finding implies that the effect of ketamine in the cerebrovascular system is related to the former cerebrovascular tone. If ventilation is not controlled adequately, increased PCO2 may cause vasodilation. Nevertheless, ICP may still increase with normal PCO2. Increased cerebral metabolic rate after ketamine administration will increase CBF.

Ketamine is showed to stimulate certain areas of the brain while inhibiting others. This is reflected by decreased CBF in areas with slow metabolism and increased CBF in high metabolism. Ketamine also affects the calcium channel so that it will increase blood flow through vasodilation. In general, racemic ketamine is related to increased CBF.[12]

The effect of racemic ketamine on cerebral autoregulation is not yet evaluated. Ketamine was proven to prevent seizure activity by its antagonistic effect on NMDA. Hypoxia and ischemia will begin cascade, activated by both NMDA and non-NMDA receptors, which leads to the membrane and cell destruction and neuronal death. When both receptors are stimulated by glutamate or aspartate, transmembrane flux and intracellular accumulation of sodium and calcium cause cell edema and activates cellular pathways. NMDA receptor antagonists are proven to be effective to prevent neuron degeneration; hence, it shows some neuroprotective profile.[12,13]

Animal studies showed a large dose of ketamine bolus and followed by continue infusion reduced the neurological deficits due to hypoxia and ischemic insults.[13] However, small bolus doses of ketamine after ischemia happened did not protect against neurological deficits. Another study mentioned that large dose of S(+) ketamine (1 mg/kg/min) is related with decreased neurological deficits, measured by plasma level of norepinephrine and dopamine, in comparison with a small dose (0.25 mg/kg/min).[11]

KETAMINE TO PREVENT OPIOID-INDUCED ACUTE TOLERANCE

Amongst the known side effect of long-term and high-dose opioid use are hyperalgesia, dependence, and tolerance. These are more pronounced in patients which experiences severe pain from malignancy, trauma, or neuropathy. Studies suggest that this may have to do with receptor desensitization and loss of receptor function. Conformational changes in opioid receptor due to phosphorylation induced by agonist increases its affinity for cytosolic β-arrestins, which in turn redistributes opioid receptors from the plasma membrane to intracellular, in a process called opioid receptor internalization. Cells are also desensitized to opioid by functional uncoupling if the μ-opioid receptors by β-arrestin.[14]

All of these mentioned processes are opioid-dependent. Painful stimuli may also produce opioid receptor internalization via NMDA receptor-mediated opioid release. This is where ketamine has a role. Pretreatment with NMDA receptor antagonists has been shown to inhibit μ-opioid receptor internalization in neurons caused by laparotomies in laboratory studies. Ketamine, in certain concentrations, interacts with phencyclidine (PCP)-binding site and inhibits NMDA receptor activity. This suggests that ketamine inhibits opioid receptor internalization.[14]

Consistent with these findings, studies in the laboratory showed that in rats, fentanyl may produce both early and long-lasting hyperalgesia and acute tolerance to morphine; however, giving ketamine as a pretreatment completely abolished this effect.[15] After intravenous administration, ketamine is metabolized into norketamine, which itself have antinociceptive action and enhance morphine's antinociceptive action. Norketamin, therefore, may support opioid analgesia and prevent both hyperalgesia and tolerance.

KETAMINE IN MAJOR DEPRESSIVE DISORDER

Studies suggest that ketamine may produce a rapid-onset antidepressant effect in patients with major depressive disorder (MDD). This is beneficial, especially given the fact that it may take weeks for the current pharmacologic treatment for MDD to be effective. Multiple studies have investigated this effect and found that the time to response was typically within hours. Administering ketamine in

rodent models produced a consistent antidepressant effect.[16]

The reason behind this remains unclear, but it is speculated to involve several target sites, namely AMPA receptor, neurotrophins, MTOR, GSK-3, GABA, and others. The unpleasant side effect of ketamine such as visual and auditory hallucinations, sedation and possible sleep disturbances, diarrhea, and impairment of certain types of memory, made it unlikely to be a first-line medication for MDD. However, these findings suggest a potential use of ketamine as a rapid-onset antidepressant.[17]

CONCLUSIONS

As time passes there are new alternative uses of ketamine, a well-established anesthetic agent. S(+) ketamine is associated with more potent and effective anesthesia with decreased side effects compared to racemic ketamine. The analgesic profile of ketamine is explored to have more benefits, such as postoperative pain control and as preemptive analgesia. The other aspect, which has been studied extensively, is the neuroprotective profile of ketamine. The administration of ketamine is not associated with increased ICP if normocapnia is achieved, making it possible anesthetic for neurosurgery. The other areas to explore include the role of ketamine to prevent opioid-induced acute tolerance and treat a major depressive disorder.

ACKNOWLEDGMENT

The author reports no conflict of interests.

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