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Ketamine: Recent evidence and current uses

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Abstract
Background: Ketamine is a dissociative anesthetic with a unique pharmacological profile that has garnered increasing interest in recent years due to its potential therapeutic uses. This review provides a comprehensive overview of the recent evidence and current uses of ketamine. The clinical uses of ketamine are summarized, including its approved and off-label uses in various anesthetic and medical conditions. Firstly, ketamine has shown efficacy as an adjunct to general anesthesia, contributing to improved analgesia, hemodynamic stability, and reduced opioid requirements. Additionally, it has demonstrated effectiveness in the management of acute and chronic pain, including postoperative pain, neuropathic pain, and cancer pain. Moreover, ketamine infusion therapy has been explored in the context of enhanced recovery after surgery (ERAS) protocols, where it has shown potential in reducing postoperative opioid consumption and accelerating recovery. The use of ketamine as a sole agent for procedural sedation, particularly in resource-limited settings, has also been investigated, highlighting its safety and efficacy. Furthermore, the emerging role of ketamine in managing opioid-tolerant and opioid-dependent patients in the perioperative period presents an intriguing area of research. The safety and adverse effects of ketamine are reviewed, including its potential cardiovascular, respiratory, and psychological effects. Finally, ongoing research and emerging evidence on ketamine are discussed, including new findings on its mechanisms of action, potential novel clinical applications, and optimization of dosing regimens. In conclusion, the reviewed literature supports the use of ketamine in various clinical settings, while acknowledging the limitations and uncertainties in its use. Continued research, evidence-based practice, and interdisciplinary collaboration are essential to help our understanding of ketamine and its potential clinical applications.

Keyword: Ketamine, Recent Evidence, Current Uses.

1. Introduction

Ketamine is a dissociative anesthetic that has been used in clinical practice for over 50 years. Originally developed as a battlefield anesthetic, it quickly became a popular anesthetic agent due to its rapid onset, short duration, and hemodynamic stability [1].

Over time, ketamine has also gained interest for its unique pharmacological properties, including its ability to produce analgesia, sedation, and dissociation. This has led to a recent surge in research on ketamine and its potential therapeutic uses. [2]

In recent years, there has been growing interest in the potential therapeutic applications of ketamine, particularly in the fields of psychiatry and pain management. The use of low-dose ketamine infusions has shown promises in treating depression, anxiety, and post-traumatic stress disorder (PTSD), while high-dose ketamine has been used to manage acute and chronic pain. Additionally, ketamine has been studied for its potential use in treating addiction, autism, and other conditions [3].

Given the growing interest in the potential therapeutic uses of ketamine, it is important to review the current evidence and understand the current clinical applications of this drug.

This review article will provide an overview of the recent research on ketamine, its unique pharmacological properties, and the current clinical uses of ketamine. By examining the current evidence, we can gain a better understanding of the potential benefits and risks associated with ketamine use and identify areas for further research and development.

Pharmacology of Ketamine:

Pharmacokinetics:

Ketamine has a rapid onset of action, typically within seconds to minutes after intravenous administration, making it an ideal agent for use in emergency situations. The duration of action is relatively short, usually between 30 minutes to an hour, due to rapid redistribution from the central nervous system to other tissues [4].

Pharmacodynamics:

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, which produces dissociative anesthesia, analgesia, and sedation. Ketamine also interacts with other receptors, including opioid receptors, serotonin receptors, and cholinergic receptors, which may contribute to its effects on mood, cognition, and behavior [5].

Metabolic Pathways:

Ketamine undergoes extensive hepatic metabolism, primarily through N-demethylation to form norketamine, which has similar pharmacological properties to ketamine. The elimination half-life of ketamine is approximately 2-3 hours, while the elimination half-life of norketamine is approximately 4-5 hours. Ketamine and

norketamine are further metabolized to hydroxylated and conjugated metabolites, which are excreted primarily in the urine [6].

The pharmacokinetics and pharmacodynamics of ketamine are important considerations in its clinical use. The rapid onset and short duration of action make ketamine an ideal agent for use in emergency situations, as well as in short procedures where a fast recovery is desired. However, the short duration of action also means that repeat dosing may be necessary to maintain adequate anesthesia, which can increase the risk of adverse effects such as respiratory depression, hypertension, and delirium [7].

The metabolic pathways of ketamine may also impact its clinical use and potential adverse effects. In patients with hepatic dysfunction, the elimination half-life of ketamine may be prolonged, increasing the risk of accumulation and toxicity. Additionally, the formation of norketamine and its metabolites may contribute to the overall clinical effects and potential adverse effects of ketamine [8]. **(Figure 1)**

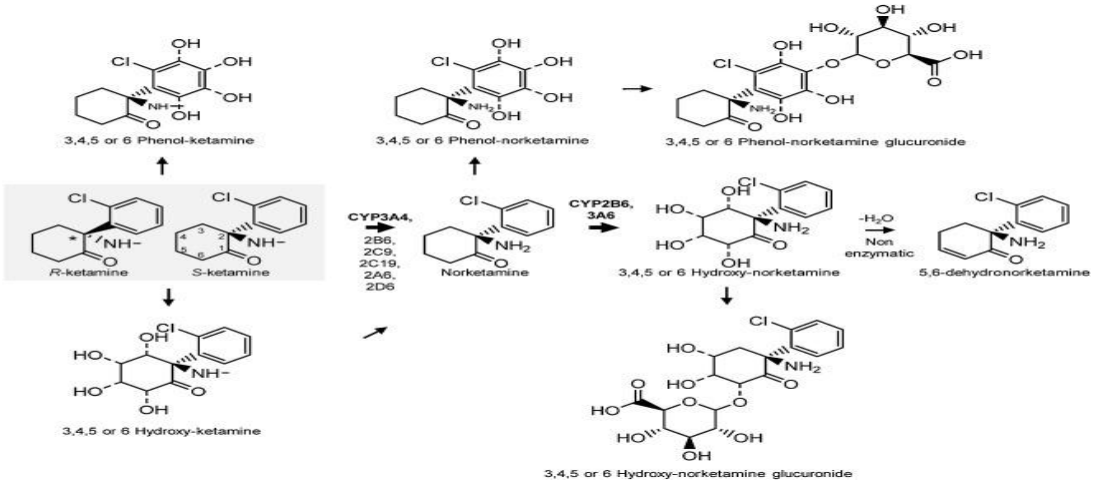

Fig. (1) Metabolism. Ketamine is metabolized mainly to norketamine (80%), itself secondarily transformed into hydroxy-norketamine (15%), mainly 6-hydroxy-norketamine. Accessory pathway passes directly through the transformation of ketamine in hydroxyketamine (5%) [9].

Overall, the pharmacology of ketamine is complex and multi-faceted, with a unique mechanism of action and metabolic pathways that may impact its clinical use and potential adverse effects. Understanding the pharmacokinetics and pharmacodynamics of ketamine is essential for safe and effective use in clinical practice [9].

Clinical Uses of Ketamine

Ketamine has been used for several decades as a dissociative anesthetic and analgesic agent. In recent years, there has been growing interest in the potential therapeutic uses of ketamine due to its unique pharmacological properties. Here is a comprehensive overview of the current clinical applications of ketamine [10]:

Approved Uses:

Ketamine is approved by the U.S. Food and Drug Administration (FDA) for use as a general anesthetic and as an analgesic in both humans and animals. In addition, ketamine is approved for use as a sedative in critical care settings, such as the intensive care unit (ICU) [11].

I. Field Anesthesia:

During the Vietnam War, ketamine was initially used as an anesthetic for injured soldiers. It quickly gained popularity due to its rapid effects, absence of hypotension or respiratory depression, and suitability for field conditions. Even today, ketamine remains the preferred choice for inducing anesthesia in the absence of an anesthesiologist and monitoring equipment [12].

II. Emergency Induction in Hypotensive Patients:

Ketamine's unique properties make it an ideal intravenous induction agent in emergency situations, particularly for patients in shock or with hypotension. Its rapid blood-cerebral transfer kinetics, sympathomimetic hemodynamic effects, and lack of adverse effects like impaired steroidogenesis provide distinct advantages. Research has shown that ketamine is a safe alternative to other agents for endotracheal intubation in critically ill patients with sepsis [11].

III. Ketamine and Brain Injuries:

Traditionally, ketamine was contraindicated for patients with brain injuries due to concerns about increased cerebrospinal fluid pressure. However, recent studies challenge this notion, suggesting that ketamine can be used as a sedative and anesthetic in patients with brain injuries under controlled ventilation. Its neuroprotective effects contribute to reduced cell death and neuronal degeneration [13].

IV. Anesthesia in Specific Conditions:

Ketamine has proven effective in providing anesthesia for patients with restrictive pericarditis and pericardial tamponade. It allows maintenance of spontaneous ventilation, bronchodilation, and preservation of the CO2 curve. Additionally, ketamine offers benefits for anesthetizing patients, especially children, with congenital heart disease, improving cardiovascular function and blood oxygenation [14].

V. Analgesia in Burn Patients:

Ketamine plays a crucial role in providing analgesia during burn dressing changes, excision and grafting procedures, and sedation. Its preservation of airway and spontaneous respiratory function makes it advantageous over other agents. Ketamine is particularly desirable for intramuscular administration in patients with extensive burns where finding suitable veins may be challenging [15].

VI. Combination Therapies:

When combined with midazolam, dexmedetomidine, or propofol, ketamine enhances sedoanalgesia and facilitates burns dressings in both adults and children. These combinations offer effective pain relief without significant side effects [16].

VII. Pediatric Premedication:

Ketamine finds utility as a premedication drug for pediatric patients through various administration routes, such as oral, intranasal, intramuscular, or intravenous. Its rapid onset of action has made it a preferred choice for induction in children and mentally challenged patients. Moreover, ketamine, alone or in combination with propofol, attenuates emergence agitation induced by sevoflurane and provides postoperative sedation, analgesia, and hemodynamic stability [17].

Ketamine's Role in Analgesia: Acute, Chronic, and Cancer Pain Management

i. Acute Pain Management:

Ketamine has proven beneficial in acute pain management, particularly when used in conjunction with opioids. By adding ketamine to opioid treatment, respiratory depression induced by opioids can be prevented, while also mitigating hyperalgesia, which increases analgesic requirements. Studies have shown that the administration of ketamine during and after surgery significantly reduces postoperative pain sensitivity and morphine requirements. Additionally, perioperative intravenous ketamine has been found to decrease analgesic consumption and pain intensity without causing adverse effects on the central nervous system. In emergency departments, low-dose ketamine combined with reduced-dose hydromorphone has been successful in providing rapid and effective pain relief in patients with acute pain [18].

ii. Chronic Pain Management:

Ketamine has gained popularity as a treatment option for chronic pain, particularly when neuropathic components are present. Despite the limited efficacy of traditional treatments, such as antidepressants, anti-epileptics, and opioids, ketamine has shown positive effects in patients suffering from chronic pain. Ketamine's ability to inhibit NMDA receptors contributes to its strong analgesic effects in neuropathic pain syndromes. Furthermore, ketamine can influence descending pain pathways involved in spinal transmission, modulating the inhibition of nociceptive input. By activating brain regions associated with descending inhibition, ketamine enhances or reactivates this inhibitory control system, providing relief for patients with peripheral neuropathy. Ketamine has been reported to reduce pain in various chronic pain syndromes, including postherpetic neuralgia, complex regional pain syndrome, cancer pain, fibromyalgia, and phantom limb pain [19].

iii. Cancer Pain Management:

Ketamine has emerged as a treatment option for cancer pain, often prescribed as an adjuvant to opioids in patients with opioid-refractory pain or dominant neuropathic pain symptoms. Ketamine's benefits in cancer pain therapy include reducing opioid tolerance, hypersensitivity to pain, and enhancing endogenous pain inhibition. By adding ketamine to the treatment regimen, patients who no longer respond to opioids or experience neuropathic pain can achieve improved pain control and relief.

Off-label Uses:

Off-label uses of ketamine include acute pain management, perioperative analgesia, treatment of refractory depression, post-traumatic stress disorder (PTSD), and other psychiatric disorders such as bipolar disorder, obsessive-compulsive disorder (OCD), and anxiety disorders. In these settings, ketamine has been used as an adjunct or alternative to traditional treatments that have failed to provide adequate relief [20].

Evidence:

The evidence supporting the use of ketamine in different clinical settings has been mixed but generally positive. In acute pain management, ketamine has been shown to provide effective analgesia and reduce opioid requirements in both adult and pediatric patients. In perioperative analgesia, ketamine has been shown to reduce postoperative pain and opioid consumption, as well as improve postoperative recovery [21].

In the treatment of refractory depression and PTSD, ketamine has shown rapid and sustained antidepressant effects, with response rates ranging from 50% to 70%. However, the optimal dosing regimen and duration of treatment are still under investigation [22].

Recent clinical trials, systematic reviews, and meta-analyses have provided valuable insights into the

efficacy, safety, and optimal dosing regimens of ketamine in different clinical settings. For example, a recent meta-analysis of ketamine for acute pain management found that low-dose ketamine (<1 mg/kg) was effective in reducing postoperative pain and opioid consumption, while high-dose ketamine (>1 mg/kg) was associated with higher rates of adverse events [23].

The administration routes and recommended doses of ketamine vary depending on the intended use. For intravenous (IV) administration, the starting dose typically ranges from 0.25 to 1 mg/kg for adults and 0.25 to 2 mg/kg for children. An alternative IV dosing range is 1 to 2 mg/kg for adults and 2 to 6 mcg·kg−1·min−1 for children. Intraosseous administration suggests a dose of 0.5 to 1 mg/kg, while an alternative dose range is 1 to 2 mg/kg. When administered intramuscularly, the recommended dose is 4 to 5 mg/kg, or 8 to 10 mg/kg as an alternative. Oral administration is an option, with doses ranging from 3 to 15 mg/kg for children and a maximum of 500 mg for adults. Lastly, intranasal administration suggests a dose of 0.25 to 4 mg/kg, or 3 to 9 mg/kg as an alternative. These administration routes and dose ranges provide flexibility in tailoring ketamine dosing to specific patient needs and circumstances. **(Table 1)**

Table (1) Routs of administration and doses of ketamines [24].

Route of administration	Starting dose
Intravenous (IV)	0.25–1 mg/kg (adults)* 0.25–2 mg/kg (children)* 1–2 mg/kg (adults)# 2–6 mcg·kg−1·min−1 (children)#
Intraosseous	0.5−1 mg/kg* 1–2 mg/kg#
Intramuscular	4−5 mg/kg* 8–10 mg/kg#
oral	3−15 mg/kg (children)* 500 mg maximum (adults)*
Intranasal	0.25−4 mg/kg* 3−9 mg/kg#

***Analgesia and sedation dose #Anesthesia dose.**

Overall, ketamine has a broad range of clinical applications, both approved and off-label. The evidence supporting the use of ketamine in different clinical settings is growing, with promising results in acute pain management, perioperative analgesia, treatment of refractory depression, and PTSD. However, more research is needed to establish the optimal dosing regimens and duration of treatment for each indication [25].

Safety and Adverse Effects:

While ketamine has shown promise as a therapeutic agent, it is important to consider its safety profile, including potential adverse effects. Here is a review of the safety and adverse effects associated with ketamine use [26]:

Potential Adverse Effects:

Ketamine can cause a range of adverse effects, including cardiovascular, respiratory, and psychological effects. Cardiovascular effects can include increases in heart rate and blood pressure, which can be particularly concerning in patients with pre-existing cardiovascular disease. Respiratory effects can include respiratory depression, particularly at high doses or when administered too rapidly. Psychological effects can include hallucinations, dissociation, and delirium [27]. **(Figure 2)**

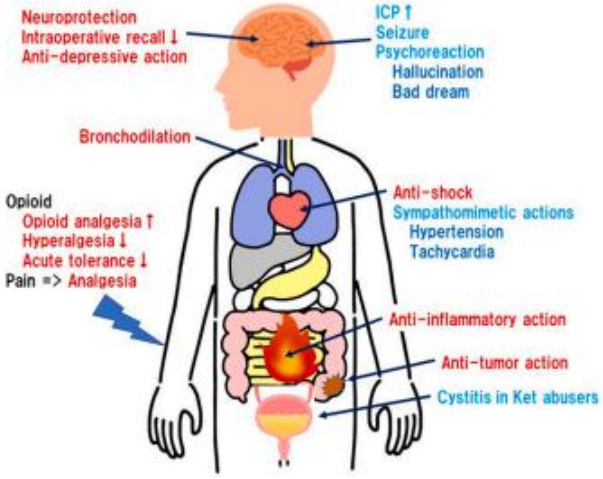

Fig. (2) Beneficial effects and adverse reactions associated with the use of ketamine [28].

Risk Factors:

The risk of adverse effects associated with ketamine use can be influenced by various factors, including patient characteristics, dose, and route of administration. For example, elderly patients, patients with pre-existing cardiovascular disease, and patients with a history of substance abuse may be at higher risk for adverse cardiovascular effects. Higher doses of ketamine or more rapid administration may increase the risk of respiratory depression and psychological effects [2].

Patient Selection, Monitoring, and Management:

Appropriate patient selection, monitoring, and management are essential in the clinical use of ketamine. Patient characteristics should be carefully considered before ketamine administration, and patients should be monitored closely for potential adverse effects during and after the procedure. Monitoring should include continuous monitoring of vital signs, including heart rate, blood pressure, and oxygen saturation, as well as assessment of level of consciousness and pain [29].

In addition, appropriate management of potential adverse effects is essential in the clinical use of ketamine. For example, if respiratory depression occurs, ventilation and oxygenation should be supported, and naloxone may be administered to reverse opioid-induced respiratory depression. If psychological effects occur, such as hallucinations or delirium, benzodiazepines or other sedative agents may be used to control symptoms [30].

Future Directions and Emerging Evidence:

Ketamine continues to be an area of active research, with ongoing investigations into its mechanisms of action and potential clinical applications. Here is an overview of the current state of research and emerging evidence on ketamine [31]:

Mechanisms of Action:

Recent research has shed new light on the mechanisms of action of ketamine, particularly its effects on the glutamate system and its ability to modulate synaptic plasticity. These findings have potential implications for the development of new therapies targeting glutamatergic dysfunction, particularly in psychiatric disorders such as major depressive disorder [32].

Novel Clinical Applications:

Emerging evidence suggests that ketamine may have potential clinical applications beyond its current approved uses. For example, recent studies have explored the use of ketamine in the treatment of neuropathic pain, opioid-induced hyperalgesia, and migraine. Additionally, there is growing interest in the potential use of ketamine in the treatment of substance use disorders, particularly alcohol and cocaine dependence [33].

Uncertainty and Controversies:

While the therapeutic potential of ketamine is promising, there are still areas of uncertainty and controversies in the current understanding of ketamine. For example, the long-term safety of repeated ketamine use is not well established, particularly in psychiatric populations. Additionally, there is ongoing debate around the optimal dosing strategies for ketamine, particularly in the treatment of depression, where there is variability in response rates and optimal dosing regimens [34].

Recommendations for Future Research and Clinical Practice:

To address these uncertainties and controversies, future research on ketamine should focus on optimizing dosing regimens, evaluating long-term safety, and exploring potential new clinical applications. Additionally, the development of clinical practice guidelines for ketamine use should consider the potential for abuse and dependence, and the importance of appropriate patient selection,

monitoring, and management of potential adverse effects [35].

Conclusion

Ketamine is a unique anesthetic with a complex pharmacological profile that has garnered increasing interest in recent years due to its potential therapeutic uses. This review has provided an overview of the current literature on ketamine, including its pharmacology, clinical uses, safety profile, and emerging evidence.

The reviewed literature supports the use of ketamine in various clinical settings, including acute pain management, perioperative analgesia, treatment of refractory depression, and other psychiatric disorders. However, there are still uncertainties and controversies surrounding the long-term safety and optimal dosing strategies of ketamine, particularly in psychiatric populations.

Overall, the current evidence highlights the potential of ketamine as a valuable tool in the management of pain and certain psychiatric conditions. However, appropriate patient selection, monitoring, and management of potential adverse effects are crucial in ensuring safe and effective use of ketamine.

Continued research and evidence-based practice are essential to further our understanding of ketamine and its potential clinical applications. Additionally, interdisciplinary collaboration between anesthesiologists, psychiatrists, pain specialists, and other healthcare professionals is necessary to ensure optimal patient outcomes and promote safe and effective use of ketamine.

In conclusion, ketamine is a promising area of research and clinical practice, and further studies are needed to optimize its use and fully understand its potential.

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