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Review article

Current applications in anesthesiology – Ketamine: Review

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ABSTRACT

Ketamine is one of the earliest hypnotic substances known with anesthetic and analgesic qualities and little suppressive effect on breathing. Clinical ketamine use started in the 1970s. Its safety and capacity to elicit analgesia and anaesthesia for a brief period were advantageous to doctors. Ketamine has been used extensively in therapeutic settings. To provide insight into the many uses and to highlight the dosage, delivery mechanism, and time course of these effects, this review integrates several basic scientific, preclinical, and clinical studies on ketamine. Ketamine's most well-known dissociative anaesthetic effects are not its only effects, it also possesses analgesic, anti-inflammatory, and antidepressant properties. The drug's clinical utility was questioned by its psychodysleptic side effects. Ketamine is still used in veterinary medicine, field medicine, and specialised anaesthesia despite these undesirable side effects. A thorough literature search was conducted using Medline, Google Scholar, and PubMed. The relevant papers' complete texts were printed and read. There is also more information about the more recent applications of ketamine and its drawbacks. Since ketamine has a lengthy history of therapeutic usage in a variety of contexts around the world due to its complicated mechanisms of action, we have examined its complex pharmacological characteristics in this review and its many uses since it was first developed. Like any review, this one is constrained by publication bias and a lack of data on unfavourable research that was not published.

Keywords: Ketamine , hypotonic substance , phencyclidine

INTRODUCTION

Ketamine, a phencyclidine derivative, is a versatile drug that produces its therapeutic effects by temporarily inhibiting the activity of N-methyl D-aspartate receptors, whose hyperactivity is the fundamental cause of painful stimulus sensitisation [1]. Ketamine is an anaesthetic created in the early 1960s and became accessible for human usage in 1970 as a rapidly acting intravenous anaesthetic agent. Since its discovery, it has been widely used. In 1962, Calvin Stevens of the pharmaceutical company Parke-Davis created ketamine for the first time by synthesising it from phencyclidine, a chemical with psychoactive, hallucinogenic, and dissociative effects. After ketamine was first administered to people in 1964 at the Michigan prison of Jackson, reports of its dissociative effects linked to brief anaesthesia began to surface [2]. Ketamine was administered to injured soldiers in a non-experimental field hospital in 1970 during the Vietnam War. Since soldiers could quickly administer ketamine to one another without requiring aid from medical personnel, it has become a popular painkiller [3].

Ketamine has a unique dissociative anaesthetic quality that enables it to be utilised successfully in a variety of situations all over the world. Its ability to quickly produce sedative, analgesic, and amnesic effects, as well as beneficial side effects like bronchodilation, airway reflex maintenance, sympathetic tone, and cardiovascular system stimulation, makes it so appealing [4]. Ketamine is recommended for postoperative analgesia and sedation because it has analgesic effects even at subanesthetic levels [5]. Ketamine is a new treatment option for people with chronic pain syndromes due to

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its capacity to modulate glutamatergic (N-methyl D-aspartate) pain receptors. Recent uses include the treatment of reactive airway illnesses, administering modest doses of analgesics, the addition of local anaesthetics to nerve blocks, and procedural sedation in operating rooms, emergency departments, and intensive care units [6]. Numerous studies have suggested that ketamine may also have fast-acting antidepressant properties, which is now categorised as a rapid-acting antidepressant beneficial in people resistant to treatment [7]. Because of the probable "emergence" phenomenon, which is characterised by vivid dreams, irrationality, delirium, and hallucinations, as well as the possibility of addiction, ketamine has not been universally embraced despite its potential benefits [8]. Studies have shown that the emergence phenomenon is more common and severe among the paediatric population, with a higher dose and longer duration of exposure [9]. Many physicians refrain from utilising ketamine despite its broad profile since studies have shown that emergence phenomena are connected with increasing patients' risk of harm and duration of hospital stay by diminishing patients' satisfaction [10]. For many years, ketamine abuse was at a very low level. However, utilisation started to increase significantly in the early 2000s. A euphoric surge, changing sensations, melting into one's surroundings, visual hallucinations, and out-of-body experiences are among the effects consumers seek [11]. The first reports of ketamine abuse date back to 1992, and as a result, the health authorities began to monitor the drug closely and added it to the list of narcotic substances in 1997 [2]. Other ketamine adverse effects include high blood pressure, nausea, vomiting, dizziness, diplopia, dysphoria, and muscular stiffness. Ketamine is not recommended for people with underlying medical disorders that might be worsened by high blood pressure, such as aortic dissection, myocardial infarction, and aneurysms [12].

METHODOLOGY

The objectives of this review are as follows: Ketamine's current use in anaesthesia and critical care. The electronic databases PubMed, Embase, Google Scholar, and Medline, were used to conduct searches of the English-language literature. Additionally, the search phrases included Ketamine, pharmacology or usage or anaesthesia or critical care. Because of their expertise and knowledge of the subject, the authors archived pertinent articles. Studies in English and research techniques using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) approach are among the requirements that articles must meet to be included in this review. Figure *1* illustrates these criteria.

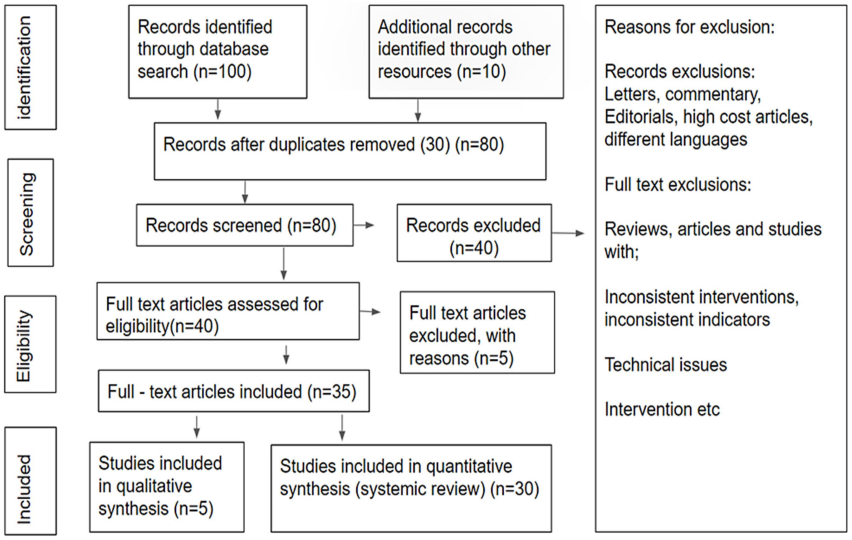

Figure 1: PRISMA model for review of literature

Pharmacology

Ketamine, a phenylcyclohexylamine derivative with mol. Wt. = 237.73 exists as two optical enantiomers, (S) and (R) ketamine [13]. Phencyclidine (PCP) was transformed into ketamine to lessen the drug's considerable psychotomimetic/psychodystolic side effects and abuse potential [14]. A noncompetitive N-methyl-D-aspartate receptor antagonist blocks the receptor's phencyclidine binding site to stop neuronal depolarization [13]. Figure *2* illustrates its chemical composition. At the C-2 carbon of the cyclohexanone ring, it has a chiral centre. The optical isomers are S-(+)-ketamine and R-(-)-ketamine. In terms of pharmacology, the S isomer is more effective. The most prevalent formulation available commercially is a racemic mixture of the two optical enantiomers [15]. S(+) enantiomer of ketamine is currently offered in a single enantiomer formulation in some nations. S(+) ketamine has four times the affinities of R(-) ketamine on the N-methyl-D-aspartate receptor and binds to μ (mu) and (kappa) opioid receptors. S enantiomer potency is three times greater than the racemic combination [16].

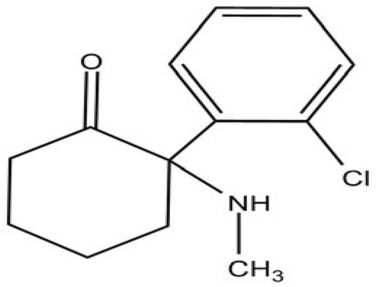

Figure 2: Chemical structure

Pharmacokinetics

Ketamine is highly lipid soluble and rapidly breaks down and redistributes to peripheral tissues, yet it has a poor capacity to bind to proteins [17]. This allows for quick passage of the blood-brain barrier. It is extensively metabolised in the liver via the N-demethylation and ring hydroxylation pathways, resulting in norketamine, a mild analgesic [14]. The demethylation of ketamine occurs in a stereoselective manner, as CYP3A4 demethylates the (S)-ketamine enantiomer more rapidly than the (R)-ketamine enantiomer, whereas CYP2B6 demethylates both enantiomers of ketamine with near equal efficiency [18]. Norketamine is further metabolised to the hydroxynorketamines (HNKs) and dehydronorketamine (DHNK) [14]. Ketamine can be administered to humans via multiple routes, including i.v., i.m., oral, intranasal, epidural, and per rectal [19]. It has a long-term impact on repeated administration, and resistance gradually develops. Ketamine is predominantly eliminated through the kidneys, where it is excreted in small amounts as ketamine (2%), norketamine (2%), and DHNK (16%). Hydroxyketamines and HNK, which are removed in urine and bile, account for most of the drug's excretion (80%) [14]. In humans, (S)-ketamine has a slightly longer elimination half-life than racemic ketamine 5 hours for (S)-ketamine versus 2-4 hours for racemic ketamine [18].

Pharmacodynamics

Central nervous system

Ketamine creates a brand-new type of anaesthesia known as dissociative anaesthesia, distinct from other anaesthetic drugs [20]. The laryngeal, corneal, and papillary reflexes are all retained throughout this trance-like cataleptic condition, and the eyes remain open. Additionally, there is some mobility and muscular hypertonia. Ketamine plasma values of 200 ng/ml, which reduce pain ratings in humans using modern functional magnetic resonance imaging, have also been shown to decrease insular cortex and thalamic activity, which are often activated by nociceptive stimulation [16].

Respiratory system

In contrast to most modern sedatives and anaesthetics, ketamine use often preserves airway tone and pharyngeal and laryngeal reflexes [13]. It has little effect on the central respiratory drive and

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promotes airway relaxation by acting on various receptors, inflammatory cascades, and bronchial smooth muscles [21]. Due to a decrease in the typical respiratory stimulating effect, elevated PaCO2 levels may have a respiratory depressing effect. This is evident after large IV boluses, which have been associated with transient episodes of apnea [13].

Cardiovascular system

The sympathetic nervous system plays a significant role in how ketamine activates the cardiovascular system, increasing heart rate, blood pressure, and cardiac output [22]. Therefore, those suffering from ischemic heart disease should be administered cautiously. Ketamine is believed to have a negative inotropic effect by preventing the reuptake of circulating catecholamines. Besides, ketamine raises blood sugar, muscle tone, plasma cortisol, and prolactin levels [8]. Additionally, it interacts with opioid receptors, monoamine, cholinergic, purinergic, and adrenoreceptor systems and has local anaesthetic effects [23].

Current clinical uses

Sedation

Ketamine is increasingly being utilised for analgesia and sedation in prehospital and emergency care. Ketamine's distinctive dissociative state can be obtained with doses ranging from 0.25 to 1.5 mg.ml-1 IV. A loading dosage given over 30-60 seconds is advised for procedural sedation in the emergency department. Sedation occurs within 1 minute and lasts 5-10 minutes. For shorter operations, a single dosage is sufficient, but for longer procedures, occasional boluses of 0.5mg.ml-1 can be used to sustain the dissociative state [24]. For induction or sedation, ketamine can be safely used with other medicines like propofol. Coadministration of these medications decreases each drug's needed dose by approximately 50%. Ketamine is thought to diminish propofol-induced hypotension through sympathomimetic effects, whereas propofol coadministration lessens the prevalence of post-procedure agitation found with ketamine alone [25]. Intramuscular, oral, or intranasal ketamine has been characterised as effective when IV access is restricted. For dressing changes, oral ketamine, combined with paracetamol and diazepam, can be used, especially in burn patients, to reduce the number of trips to the operating room.

Induction and maintenance of anaesthesia

For rapid sequence induction, an IV dosage of 1 to 2 mg.kg-1 can create dissociative anaesthesia in 1 to 2 minutes, which is faster than typical IV induction drugs like propofol or thiopentone. Ketamine, however, provides significant advantages when haemodynamic management is critical, such as trauma or sepsis. Cardiogenic shock, hypovolaemia, and pericardial tamponade are all possible indications for ketamine TIVA, especially in low-resource countries where the availability of vasoactive medications may be limited. Ketamine TIVA has also been used successfully in paediatric anaesthesia [26].

Analgesia

At lower dosages, ketamine has been demonstrated to desensitise central pain pathways and modify opioid receptors, making it a potent analgesic. Ketamine is a beneficial drug for treating trapped casualties or even mass casualties [27]. Ketamine is used with opioids like morphine or transmucosal fentanyl to aid combat medics in handling pain without the danger of hypotension caused by the opioid. Evidence suggests ketamine may benefit chronic opioid users having surgery due to the desensitisation of central pain pathways [28]. Ketamine provides analgesia during burn dressing changes, excision and grafting procedures, and sedation. The main benefit of ketamine in burns is that, unlike other analgesics, it typically retains airway and spontaneous respiratory function while also delivering excellent sedoanalgesia [26].

Reactive airways

Due to its bronchodilating effects, ketamine is helpful in patients with acute bronchospasm. Ketamine treatment for acute bronchospasm improved minute ventilation, decreased inspiratory pressures, and gas exchange in mechanically ventilated patients receiving these treatments. These patients were also frequently successfully weaned off support [29].

Uses in critical care

Ketamine may be used in critical care medicine for sedation, analgesia, and the treatment of chronic bronchospasm, to name just a few applications. A continuous IV infusion of ketofol provides suitable and secure short-term sedation (24 hours) for critically ill patients in the ICU [30]. Due to its cardiovascular stimulatory effects, ketamine lowers inotropic support in septic patients with circulatory

instability and has a protective antiinflammatory influence against the sepsis process [31].

Newer uses

Ketamine has been shown to enhance the efficiency of paediatric caudal anaesthesia when combined with a dose of 0.5-1 mg/kg local anaesthetic. Ketamine alone or in combination with propofol lessens sevoflurane-induced emergence agitation in paediatric patients [3]. Stellate ganglion blocks and peripheral nerve blocks are utilised in addition to IV regional anaesthesia (IVRA). Tourniquet tolerance is increased, anaesthesia quality is improved, and analgesic consumption is decreased with IVRA using 0.1 mg/kg ketamine in 0.5 per cent lignocaine or 0.5 mg/kg ketamine in 1 per cent lignocaine. Low-dose regimens have been suggested as an adjuvant for postoperative analgesia and lowering exogenous opioid-induced hyperalgesia. These regimens typically consist of an initial bolus of 0.25 to 0.5 mg/kg administered intravenously, followed by 50 to 500 g/kg/h. Ketamine may help with migraine, fibromyalgia, chronic regional pain syndrome (CRPS), visceral pain, chronic peripheral and central neuropathic pain, and phantom and ischemic limb pain [3]. Ketamine has been employed as a co-analgesic in palliative care in addition to opioids and co-adjuvant medications. The World Health Organization has included ketamine on its list of essential medications for patients who no longer respond to high doses of opioids or who have anticipated breakthrough pains since it is currently regarded as an essential adjuvant analgesic for refractory cancer pain. Initial oral dosages for analgesia range from 2 to 25 mg administered three to four times daily, progressively increasing to 40 to 60 mg administered four times daily. 2.5-5 mg of analgesia are administered intravenously as needed, and 0.5-1 mg/kg is given for painful procedures. SC dosages typically range from 2.5 to 25 mg, with continuous SC injection beginning at 50 to 100 mg every 24 hours and up to 600 mg every 24 hours as needed [32]

Miscellaneous applications

With ketamine sedation, ischemia-reperfusion injury can be minimised during spinal anaesthesia for arthroscopic knee surgery [33]. According to studies, s-ketamine decreased the number of ECT treatments, produced lower depression severity scores, and enhanced cognitive evaluations. After surgery, a ketamine gargle soothes sore throat [34]. Patients have used it to cure hiccoughs, acute intermittent porphyria, and liver damage [35]. Additional research has demonstrated that ketamine decreases suicide ideation in people with serious depression. Due to its ability to suppress the generation of excessive proinflammatory cytokines, ketamine treatment before or during surgical procedures has been utilised to improve postoperative outcomes. Anti-inflammatory effects (i.e., a decrease in proinflammatory cytokines) of 0.15-0.25 mg/kg (single i.v. bolus) of preoperative subanesthetic doses [8].

Drawbacks of ketamine use

Ketamine is inappropriate for operations requiring muscle relaxation due to its increase in muscular tone. Ketamine is inappropriate for operations requiring muscle relaxation due to its increase in muscular tone. Ketamine abuse is a possibility. Absolute contraindications to IV ketamine include hypertension, pregnancy or eclampsia, significant heart disease, stroke, high intracranial pressure, and acute porphyria. The epidural and spinal routes of ketamine administration are normally not recommended due to their uncertain toxicity [35].

CONCLUSION

Due to its complex modes of action, ketamine has a lengthy history of usage in therapeutic settings worldwide. Ketamine is used more frequently for pain management and palliative care rather than just anaesthesia. Most of the ketamine's therapeutic benefits are believed to be primarily caused by the drug's antagonistic actions on the NMDA receptor. Due to ketamine's solubility in lipid and water solutions can be administered effectively by intravenous, intramuscular, subcutaneous, transdermal, sublingual, and intraosseous routes. Ketamine is effective as an anaesthetic in prehospital settings, trauma patients with hemodynamic compromise, military services for injured troops, and children needing sedation for unpleasant or frightening surgeries in the Emergency Department. Ketamine use in the perioperative setting has been associated with reduced opioid need, postoperative nausea, and vomiting and has no major adverse effects. Furthermore, giving ketamine to surgical

patients experiencing excruciating postoperative pain has demonstrated promising results.

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