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Overview of Ketamine Activity in General Anaesthesia

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Abstract: *The administration of intravenous agents is the most used method in Canada and the United for the purpose of producing general anesthesia or sedation for dental procedures. Some of the pharmacokinetic, pharmacodynamic, and physical characteristics of ketamine, a dissociative anesthetic, are favorable. It can cause amnesia, sedation, analgesia, and anesthesia. Ketamine can maintain functional residual capacity, induce bronchodilation, and avoid cardiovascular depression. However, adverse effects have been demonstrated, such as cardiovascular stimulation and unpleasant emergence phenomena, both of which may be modulated by supplementation with benzodiazepines. An increase in the Ketamine has lately been promoted for use in ambulatory anesthesia. The use of ketamine as an effective agent for specific anesthetic procedures is supported by this review of the literature*

Keywords: anesthesia

I. INTRODUCTION

Ketamine has become more common in the prehospital, emergency room, and operating theatre setting, however, its role is not well defined. Ketamine is a strong anesthetic and dissociative analgesic. Proponents advocate that its properties are appealing in many awkward clinical scenarios. In this non-systematic review, we present useful concepts based on the available literature and our clinical experience gathered in America, Canada, Australia, and Europe. Ketamine is a used as a treatment for depression and in pain management, ketamine induces a state of Dissociative anesthesia is a trance-like condition that induces amnesia, sedation, and pain relief. The US Food and Drug Administration (FDA) has authorized ketamine hydrochloride, also referred to as ketamine, for use as a general anesthetic either alone or in conjunction with other drugs.

The medication is highly effective for brief medical procedures that do not necessitate skeletal muscle relaxation and can be utilized as a pre-anesthetic for the induction of general anesthesia when combined with other general anesthetic agents. Furthermore, ketamine is FDA-approved for enhancing the effects of low-potency substances such as nitrous oxide. The ketamine molecule [2-(O-chlorophenyl)2-methylamino cyclohexanone] has a molecular weight of 238g/mol. and C13H16ClNO, the molecular formula for ketamine. Ketalar is the brand name of this drug. One type of anesthetic is ketamine. It helps people fall asleep both before and during surgery.

In addition to its anesthetic applications, ketamine proves invaluable in pain management, addressing treatment-resistant depression, managing suicidal ideation, and treating refractory status epilepticus, with specific indications. The dosage determines the application and resulting effects of the drug, leading to variations in the prescribing protocol. This versatility renders ketamine valuable in both anesthesia and pain management. Ongoing research explores the potential applications of ketamine in psychiatry across all isomeric forms. At elevated doses, ketamine operates primarily as a sedative rather than an analgesic agent. This activity reviews ketamine's indications, mechanism of action, pharmacokinetics, adverse drug reactions, monitoring strategies, drug-drug interactions, and clinical toxicology for healthcare professionals to facilitate the enhancement of clinical best practice guidelines.

The use of ketamine in anaesthesia reflects its characteristics. It is a drug of choice for short-term procedures when muscle relaxation is not required. The effect of ketamine on the respiratory and circulatory systems is different from that of other anaesthetics. It suppresses breathing much less than most other available aesthetics. When used at anaesthetic doses, ketamine usually stimulates rather than depresses the circulatory system. Protective airway reflexes

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are preserved, and it is sometimes possible to administer ketamine anaesthesia without protective measures to the airways.

Ketamine is an option in children as the sole anesthetic for minor procedures or as an induction agent followed by neuromuscular blocker and tracheal intubation. Children with cyanotic heart disease and neuromuscular disorders are good candidates for ketamine anesthesia. Due to the bronchodilation properties of ketamine, it can be used for anesthesia in people with asthma, chronic obstructive airway disease, and with severe reactive airway disease including active bronchospasm. The unique properties of the ketamine along with its wide versatility in appropriately suitable with prehospital and emergency medicine, and gain benefit of those unique properties by anaesthetists or their assistants around the world who are using ketamine.

History of Ketamine

-The first human clinical study was performed in 1964, followed by the introduction into clinical use as early as 1970. Ketamine was first used as a battlefield anaesthetic, for uncooperative children and in veterinary medicine. The history of ketamine begins in the on March 26 1950s at Parke-Davis and Company's laboratories in Detroit, Michigan, USA. At that time, Parke-Davis was searching among cyclohexylamines for an 'ideal' anaesthetic agent with analgesic properties. Ketamine and propofol are currently listed as the two injectable medicines under general anaesthetics in the WHO Model List of Essential Medicines. First compiled in 1977, the Model List is updated and revised every two years; ketamine was added in 1985. Medications on the list are determined by a committee to "satisfy the health care needs of much of the population; they should therefore always be available in adequate amounts and in the appropriate dosage forms, and at a price that individuals and the community can afford. The ease of administrating and monitoring ketamine makes it an attractive alternative in developing countries where the facilities may be suboptimal; as a result, it is often the only available anesthetic for use.

Parke-Davis then investigated the potential of phencyclidine as a human anaesthetic under the trade name of Sternly (Parkes-Davis). In 1958, the first human trials of PCP (Sternly) were published by Dr Greifenstein (1915 to 1997), professor of anaesthesiology at the Wayne State University, Detroit. PCP caused increases in blood pressure, respiratory rate and minute volume, with conservation of corneal and laryngeal reflexes. The presence of nystagmus and increased salivation were noted. These studies revealed genuine narcosis, with a cataleptic state, potent amnesia and analgesia produced by ketamine anaesthesia. Greifenstein and John Stirling Meyer, head of neurology at Wayne State University, concluded that phencyclidine produced a 'centrally mediated' sensory deprivation syndrome.

Routes of Administration: –

Ketamine may be administered by a variety of routes as it is both water and lipid soluble. Intravenous, intramuscular, oral, rectal, subcutaneous, epidural, and trans nasal routes have all been used. Following intravenous administration bioavailability is 90%, but by the oral or rectal routes bioavailability is only 16%. After oral administration there is a delay in achieving peak effect compared to intravenous administration (15–30 min compared with 1–5 min) and peak serum concentrations are only ones fifth of those found after parenteral administration. These differences are due to incomplete gastro-intestinal absorption and first pass metabolism. Following oral administration of ketamine, nor ketamine levels are three times higher than with intravenous administration and this is thought to have a significant role in the analgesic effects of oral ketamine. Ketamine may be used epidurally either as an adjunct to local anaesthetics or alone. It binds to NMDA receptors in the dorsal horn of the spinal cord and greatly prolongs the analgesia provided by single-shot epidural techniques. Early attempts to use ketamine epidurally produced neurotoxicity. This was demonstrated to be due to the preservative used in epidural preparations. The preservative-free ketamine preparation must be used for epidural administration. (https://images.app.goo.gl/MbyAy8tmgNdVVZMHA).

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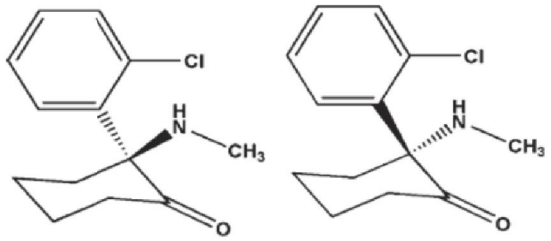
Administration Route	Dose
Intravenous	0.15–0.3 mg/kg bolus 0.15–0.3 mg/kg/h infusio
Intramuscolar	0.5–1 mg/kg
Intranasal	1 mg/kg
Oral	0.5 mg/kg every 12 h
Transdermal	25 mg/24 h
Subcutaneous	0.05–0.15 mg/kg/h
Rectal	10 mg/kg

Isomers of Ketamine: -

The chiral centre of the cyclohexanone ring permits the existence of two enantiomers. Ketamine enantiomers exhibit pharmacological and clinical differences. S-(þ)-ketamine has greater affinity than R-(2)-ketamine at phencyclidine binding sites on the NMDA receptor. There are no significant differences in pharmacokinetic properties between enantiomers and the racemic mixture. S-(þ)-ketamine has been shown to be twice as potent as the racemic mixture in producing anaesthesia and analgesia, and thrice as potent as R–ketamine. Animal studies suggest that the R- enantiomer of ketamine is a more potent relaxant of acetylcholine induced airway smooth muscle contraction than the S(þ) enantiomer. This difference appears to be caused by differential actions on receptor linked calcium channels. This may have implications in the management of patients with asthma. Clinical studies have shown that the recovery time is reduced with S-(þ)-ketamine compared with the racemic mixture.

more expensive than the generic, racemic ketamine. Ketamine and its (S)-enantiomer show distinct psychological effects that are investigated in psychiatric research. Its antidepressant activity may depend on the extent and quality of these psychological effects which may greatly differ between the enantiomers, (S)-ketamine isomer is a more potent aesthetic than (R)-ketamine.



R-(–)- ketamine *S*-(+)- ketamine

FIGURE1-Chemical structural of the two ketamine enantiomers.

Mechanism of Action:

Ketamine's mechanism of action is widely regarded as one of pharmacology's most complex due to its interaction with multiple binding sites including NMDA receptors, opioid receptors, Na channels, and L-type calcium channels. The action of ketamine is mainly caused by its blockade on the N-methyl-D-aspartate (NMDA) receptors which are one kind of glutamate receptor in the action, blocking these receptors leads to impaired pain signal transmission and changes in brain function, resulting in its anesthetic, analgesic and dissociative effects. Ketamine binds non-competitively to the phencyclidine recognition site on N-methyl-D- aspartate (NMDA) receptors. In addition, ketamine exerts effect at other sites including opioid receptor & muscarinic receptors & nicotinic acetylcholine receptors, Ketamine's neuropharmacology is complex NMDA receptor subtype of glutamate gated ion channels with reduced single-channel conductance, low calcium permeability and low voltage-dependent sensitivity to magnesium. Pharmacological characterization of glycine-activated currents in HEK 293 cells expressing N-methyl-D-aspartate NR1 and NR3 subunit.

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The mechanism of action of ketamine in alleviating depression is not well understood, and is an area of active investigation. Due to Ketamine was created as an antidepressant with the theory that its antidepressant effects are caused by NMDA receptor antagonism. However, it is unclear if ketamine by itself has antidepressant effects or if its metabolites play a significant role.

The active metabolite of ketamine, which does not significantly interact with the NMDA receptor but nonetheless indirectly activates AMPA receptors, may also or alternatively be involved in the rapid-onset antidepressant effects of ketamine. Stimulates opioid receptors and is thus a unique sedative agent in that it provides analgesia as well the thalamocortical projection system is the primary location of central action. Thus, it selectively inhibits neuronal function, especially in the thalamus and areas of association, whileat the same time activating the limbic system, which includes the hippocampus, causing a functional disarray of non-specific pathways in the thalamic area and midbrain. The phrase "dissociative anesthesia" originates from the fact that it also inhibits the transmission of impulses in the medullary reticular formation, a crucial structure in the transfer of the emotional affective components of pain perception from the spinal cord to the higher canters of the brain.

Drugs like phencyclidine and ketamine can inhibit the interaction with the NMDA (N-methyl-d-aspartate) receptors, which is necessary for this activity. Some of its analgesic effects on the central nervous system (brain and spinal cord) may be explained by evidence of opioid receptor occupation in the brain and spinal cord (the S enantiomer acts on the mu receptor).

Therefore, cross tolerance between opiates and ketamine may be anticipated because of the presence of a shared receptor. Although Stella et al. found dysphoric reactions to emersion in research involving 68 adults who were premedicated with naloxone for general surgery, this idea would receive more support if naloxone reversed its effects in humans. Stimulation of the sigma opioid receptors is one theory There is also evidence of stimulation of the muscarinic/nicotinic cholinergic receptors, serotonin, dopamine and norepinephrine receptors, type-L calcium channels and sodium channel.

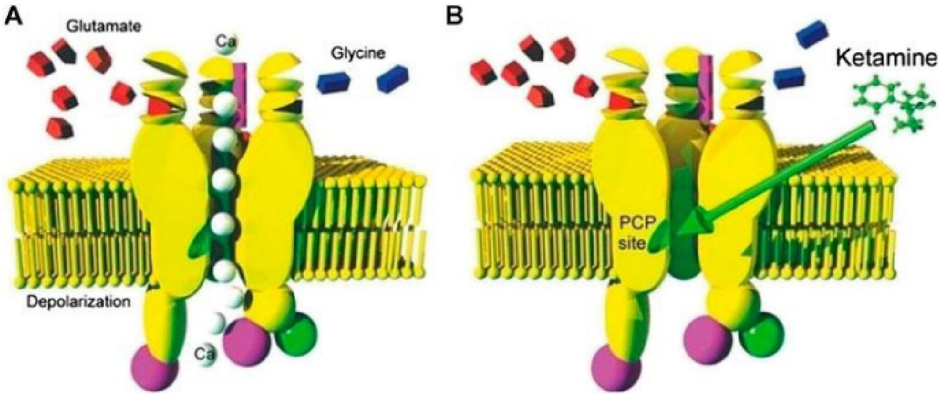

FIGURE 2- Depiction of an NMDA Receptor in the open state and allowing passage of calcium ions due to binding of glutamate and or glycine **(B)** An image of an NMDA receptor blockaded by binding of ketamine due to binding of the drug at the PCP binding site.

Ketamine's Role in General Anaesthesia: -

Ketamine is a multipurpose drug whose special qualities make it an important part of general anesthesia. This special intravenous (IV) anesthetic has a broad range of pharmacological effects, such as sedation, catalepsy, somatic analgesia, bronchodilation, and stimulation of the sympathetic nervous system.

Anaesthetic Properties: A drug used to induce anesthesia in other words, to result in a temporary loss of sensation or awareness. They may be divided into two broad classes: general aesthetics, which result in a reversible loss of consciousness, and local aesthetics, which cause a reversible loss of sensation for a limited region of the body without necessarily affecting consciousness.

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Dissociative Anesthesia -The effects of dissociative can include sensory dissociation, hallucinations, mania, catalepsy, analgesia, and amnesia. Ketamine induces a state of dissociative anesthesia, characterized by a disconnection between the mind and body. This results in a trance-like state with minimal pain perception and amnesia.

Rapid Onset: Ketamine acts quickly, making it ideal for emergency situations or when rapid induction of anesthesia is required.

Minimal Respiratory Depression: Unlike many other aesthetics, ketamine does not significantly depress respiration, making it useful for patients with respiratory compromise.

Bronchodilation: Ketamine has bronchodilators properties, which can be beneficial for patients with asthma or other respiratory conditions Analgesics, also called painkillers, are medications that relieve different types of pain killers from headaches to injuries to arthritis. Anti-inflammatory analgesics reduce inflammation, and opioid analgesics change the way the brain perceives pain. Some analgesics can be bought over the counter, others require a prescription.

Potent Analgesia: Ketamine provides powerful pain relief, both during and after surgery.

Prolonged Analgesia: Its analgesic effects can last for several hours, reducing the need for additional pain medications. Ketamine is a phencyclidine derivative that produces dissociative anesthesia characterised by evidence on the EEG of dissociation between the thalamocortical and limbic system.

Pharmacological Effect of Ketamine: -

Central Nervous System Effects-

The major effects of ketamine administration involve the CNS. This agent produces a unique state that has been described as "dissociative anesthesia" and is characterized by profound analgesia, amnesia, and catalepsy. The anesthetic state produced is frequently called “dissociative anesthesia” which implies that the patient is detached from the environment and sel.

The term "dissociation component" describes the functional and electrophysiological division of the limbic and thalamone cortical systems. It is thought that this condition results from a breakdown in regular contacts between the sensory cortex and the association areas, which prevents the brain from correctly transducing afferent impulses. The outcome is like cataracted, where the eyes may stay open with intact corneal reflexes and sluggish nystagmus. Despite their apparent alertness, patients are typically noncommunicative. Skeletal muscle hypertonus can occur in different degrees. Non purposeful skeletal muscle movements may occur irrespective of surgical stimulation. It is frequently challenging to evaluate a distinct endpoint when ketamine is given, in contrast to the use of intravenous barbiturates for the induction of anesthesia.

To produce its effects, ketamine probably interacts with multiple pharmacologic receptor types. Opioid receptors at the brain, spinal cord, and peripheral locations seem to be at least partially responsible for the analgesia. Ketamine predominantly binds to opioid receptors that are mu rather than delta. Ketamine enhances the effects of neuromuscular blocking medications in a dose-dependent way in addition to its own effects.

The N-methyl-D-aspartate (NMDA) receptor has been proposed as the site of action for ketamine. Due to their interactions with excitatory amino acid neurotransmitters, these receptors are believed to mediate the excitation of neurons in the central nervous system and play a significant part in the transmission of sensory information. The effect of ketamine treatment is consistent with catalepsy caused by NMDA inhibition. Since ketamine has been demonstrated to be a strong noncompetitively NMDA antagonist, this may be the mechanism behind its behavioural and anesthetic effects.

Ketamine increases cerebral blood flow by 62%22 to 80% by powerfully vasodilating cerebral blood channels. Consequently, in patients with impaired intracranial compliance, this is the cause of observed elevations in intracranial pressure. If diazepam, midazolam, or thiopental are given prior to ketamine, this impact is lessened. However, the usage of ketamine is constrained by elevated cerebral fluid pressure. In contrast to the general anesthesia created by other substances that mimic regular sleep, ketamine causes a cataleptic state. The pupils dilate moderately, nystagmus appears, tearing, salivation, and head and limb movements occur, but almost none of these side effects occur when it is used at sub-anesthetic doses for the treatment of chronic pain. These patients have profound analgesia, but their eyes stay open and they retain many reflexes (corneal, tussigenic, swallowing), which should not be interpreted as protective.

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Respiratory Effects-

When compared to other anaesthetics, ketamine treatment produces peculiar responsive responses. When most general anesthetic medications are administered to patients who are breathing on their own, the functional residual capacity (FRC) immediately decreases, increasing the arterial-alveolar oxygen difference. The tiny, thin-walled airways in the dependent areas of the lungs have a propensity to collapse as lung volume drops during expiration. The closing capacity is the volume at which airway closure takes place. Ensuring the inflation of these dependent lung segments is the result of FRC maintenance. Since the closure capacity in children is closer to the FRC than it is in adults, this is very crucial.

Adults. Small reductions in FRC in children may cause airway closure during normal tidal breathing, leading to anomalies in ventilation-perfusion that are clinically manifested as a fall in oxygen saturation. Ketamine seems to be special in that it can keep FRC stable when anesthesia is induced, which lowers the risk of intraoperative hypoxemia. Patients who are breathing on their own under ketamine anesthesia may have their minute ventilation kept at the same amount as when they are awake. Additionally, there might not be any atelectasis or shunting, and there might be just slight alterations in gas exchange. It seems that atelectasis or alterations in ventilation-perfusion and FRC do not occur under ketamine anesthesia because skeletal muscle tone is preserved (unlike with the volatile drugs).

Due to the inability to provide positive airway pressure, the anaesthesiologist has less control over these changes in spontaneously breathing patients than in mechanically ventilated ones. This is crucial for dental anesthesia because variations in any of these factors may cause the oxygen saturation level to drop. There is debate over ketamine's overall impact on breathing. Ketamine has been shown in studies to have both respiratory stimulant and respiratory depressant properties. But the only study that seemed to accurately measure the ventilatory response was the one that demonstrated ketamine to be a respiratory depressive.

Other positive effects of ketamine on the respiratory system include reduced airway resistance and improved lung compliance. It is currently unknown what mechanism underlies these effects. Histamine, acetylcholine, potassium chloride, propranolol, and indomethacin all have little effect on ketamine-induced bronchodilation, despite each of these substances implicating a different mechanism affecting bronchial tone. Ketamine may have the ability to block calcium channels by inhibiting extracellular calcium transport in a dose-dependent manner.

Although ketamine is said to preserve laryngeal tone and reflexes, pulmonary aspiration has been documented in certain instances.

Cardiovascular Effects-

Ketamine differs from most anesthetic agents in that it appears to stimulate the cardiovascular system, producing increases in heart rate, cardiac output, and blood pressure.

Since ketamine has been demonstrated to directly reduce myocardial contractility, the mechanism underlying this effect is not well known.

Alpha and beta receptors antagonists, as well as the calcium-channel blocker verapamil, can prevent the observed cardiovascular stimulation. Central sympathetic activation is probably what masks the direct negative inotropic impact of ketamine in clinical settings. Alternatively, the negative inotropism may be overcome by ketamine's capacity to raise circulating catecholamine concentrations, presumably by preventing neuronal reuptake. These effects are said to be lessened by benzodiazepines.

Patients with severe ischemic heart disease should not use ketamine because the sympathomimetic effects are likely to raise myocardial oxygen demand. Furthermore, patients who should not have their blood pressure raised, such as those who have had a significant hypertension or cerebrovascular accident in the past, should not take ketamine due to its cardiovascular-stimulating effects.

Additionally, individuals who should not have their blood pressure raised, such as those who have a history of severe hypertension or cerebrovascular accidents, should not take ketamine due to its cardiovascular-stimulating effects.

Although certain animal studies indicate that ketamine sensitizes the myocardium to the dysrhythmogenic effects of epinephrine, cardiac dysrhythmias are rare after ketamine administration. There is currently no solid data regarding how ketamine affects cardiac rhythm.

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There is currently no solid data regarding how ketamine affects cardiac rhythm. Ketamine has been promoted for use in young patients with cyanotic congenital heart disease, hypovolemic patients, and those in cardiogenic shock because of its cardiovascular benefits, especially its capacity to maintain arterial blood pressure.

The pulmonary blood flow in children with cyanotic congenital heart disease affects how much oxygen the lung can absorb. Ketamine has been utilized to maximize arterial oxygen tension and pulmonary blood flow by reducing right-to-left intracardiac shunting.

Anesthesia Effect

Ketamine's properties are reflected in its application in anesthesia. When muscular relaxation is not necessary for brief procedures, this medication is the preferred option. Ketamine has a distinct effect on the circulatory and respiratory systems compared to other anaesthetics. Compared to many other anaesthetics on the market, it suppresses respiration considerably less.

Ketamine typically stimulates the circulatory system rather than depresses it when given at anaesthetic levels. It is occasionally possible to deliver ketamine anesthesia without taking precautions to protect the airways, and protective airway reflexes are maintained. Ketamine's acceptability is restricted by psychotomimetic effects; however, lamotrigine and nimodipine reduce these effects and can also be offset by the administration of benzodiazepines or propofol.

Ketamine is commonly administered to individuals with serious injuries and seems to be safe for them.

During the Vietnam War, for instance, it was extensively utilized for emergency surgery in combat zones. The use of ketamine as a sedative in emergency medicine, even during physically taxing procedures, is supported by a 2011 clinical practice guideline. For those in severe shock who run the danger of hypotension, it is the recommended medication. Since ketamine can elevate blood pressure, it is frequently helpful in treating serious head injuries. It is unlikely to drop blood pressure, which is problematic for those who have experienced such traumas

Due to the bronchodilation properties of ketamine, it can be used for anesthesia in people with asthma, chronic obstructive airway disease, and with severe reactive airway disease including active bronchospasm.

Analgesic Effect-

In emergency rooms and during the surgical phase for patients with intractable pain, ketamine infusions are used to relieve acute pain. The doses are typically referred to as sub-anesthetic doses because they are lower than those used for anesthesia. Ketamine, either alone or in combination with morphine, lowers postoperative morphine use, pain, nausea, and vomiting. Patients with opioid tolerance and surgical patients who anticipate significant post-operative pain are likely to benefit from ketamine the most.

Ketamine's efficacy and low risk of respiratory depression make it particularly helpful in pre-hospital settings. When it comes to treating acute pain and controlling procedural pain in a hospital emergency room, ketamine is just as effective as opioids. Additionally, it might stop postanaesthetic shivering and opioid-induced hyperalgesia. Ketamine is used as an intravenous analgesic for chronic pain, primarily neuropathic pain. Additionally, it counteracts wind-up phenomena, which are caused by spinal sensitivity and chronic pain. Ketamine infusions provided short-term pain alleviation for fibromyalgia, complex regional pain syndrome (CRPS), neuropathic pain, and pain following traumatic spine injury in several clinical trials.

Ketamine is commonly used as an analgesic in emergency medicine and as an adjuvant drug in the perioperative setting. In addition, it is used as a third-line adjuvant drug for opioid-resistant pain inpalliative care and for intractable chronic noncancer pain. More recently, ketamine is increasingly being used to treat major depression and other mood disorders. There is a large body of literature addressing the use of ketamine in the perioperative setting. Adjuvant treatment with IV racemic, or S (+) ketamine is common, to improve postoperative pain relief and reduce opioid requirements. Epidural ketamine has also been used in this setting. In some cases, ketamine has been used with the aim of preventing chronic postoperative pain.

Only informational reasons are served by this. See a professional for diagnosis or medical advice. Although its primary usage is as an anesthetic, the drug ketamine also has pain-relieving effects. It functions by preventing pain signals from being sent through the brain's NMDA receptors. Numerous chronic pain disorders, such as complex regional pain syndrome (CRPS), fibromyalgia, neuropathic pain, and post-surgical pain, can be treated with ketamine. Although it

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can be taken orally or intranasally, ketamine is usually given intravenously or intramuscularly. Ketamine's most frequent adverse effects
include light headedness, nausea, and vomiting. Hallucinations and other dissociative symptoms are potentially possible side effects of ketamine use.

Immunoinhibitory Effects

Effects of immune inhibition Immunoinhibitory effects have been observed in vitro in the laboratory and in the clinical setting of sepsis patients in recent years, making it likely the most studied characteristic. Anti-inflammatories have been shown to modulate innate immunity and pro-inflammatory signalling with down-regulation of the increase in expression of sepsis-induced TLR2/4.

Ketamine can raise arterial pressure and preserve circulatory stability in clinical settings, mostly via inhibiting the release of pro-inflammatory cytosines. Additionally, it affects the synthesis of cortisol, the metabolism of tryptophan, and bioproducts such kynurenine, which is known to modulate the actions of NMDA receptors.

Among the various methods that suppress the activation of nuclear factor NF-kB and the genetic production of TNF-a and IL-6 is most likely the alteration of this signalling pathway. According to other research, the inhibition of nitric oxide synthetase activity induction and the reduction of endotoxin-generated protein expression may influence vital physiological and psychological processes. The medication reduces the inflammatory response brought on by lipopolysaccharides (LPS) in a dose-dependent manner. Additionally, the kinase pathway-regulated extracellular signals and cell cycle arrest-induced proliferation of carcinomatous cells are inhibited by the NMDA receptor. By limiting chemotactic activity and reducing oxidant generation, one can also impair the function of neutrophils, and lymphocytes.

Since surgical trauma may cause a complex cytokine cascade with varying consequences on the patient, ketamine triggers immunological responses in individuals undergoing surgery. While cell-mediated immunity is inhibited, the immune system's pro-inflammatory cytokines are overstimulated. Therefore, if the inflammatory response is out of proportion, patients may be compromised by some undesired outcomes like low blood pressure, shock, and multiple organ failure. Given that pro-inflammatory cytokines and pain perception are known to interact and regulate one another, it is critical to reduce the suppression of the lymphocyte-mediated immune response and attenuate the pro-inflammatory cytokine response to surgery through effective pain management. This will lessen the post-operative response to surgical stress.

Benefits Of Ketamine: -

- Ketamine therapy offers swift pain relief by blocking NMDA receptors, disrupting pain signals and reducing pain perception.
- Ketamine provides rapid relief from depression and mood disorders by blocking NMDA receptors and promoting the release of Brain-Derived Neurotrophic Factor (BDNF), potentially offsetting symptoms within hours.
- Ketamine therapy explores treatment possibilities for conditions like PTSD, OCD, and chronic pain, which are often resistant to conventional medications.
- Ketamine therapy is particularly effective for individuals with treatment-resistant depression, offering hope to those who have not responded well to other treatments.
- Although the immediate effects wear off, ketamine therapy can provide longer-lasting symptom relief, sometimes extending for weeks or even months after treatment.
- Ketamine may promote neuroplasticity, helping the brain rewire itself and establish healthier patterns of thinking and behaviour.
- Ketamine therapy may reduce dependence on other medications, potentially allowing for lower doses of antidepressants and minimizing their side effects, all under professional supervision.
- Ketamine may have anxiolytic qualities, according to some study, which could help reduce the symptoms of anxiety disorders.

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- Some people have reported feeling less anxious after using ketamine, especially those who suffer from social anxiety disorder or generalized anxiety disorder. People who don't react well to other therapies may find comfort from its frequently rapid effects.
- Ketamine may promote the growth of new neurons in the brain, which could contribute to its antidepressant effects.
- It can enhance the brain's ability to form new connections between neurons, potentially leading to improved cognitive function and mood regulation
- Can be used as an adjunct to other pain medications to increase their effectiveness.

Disadvantages Of Ketamine

- People with cardiovascular disorders may be at risk since ketamine can increase heart rate and blood pressure.
- Prolonged or high-dose use of ketamine can lead to urinary retention and bladder problems.
- Vomiting and nausea are frequent adverse effects, especially when taking larger dosages.
- A dissociative condition brought on by ketamine can cause feelings of disassociation from one's body and environment. For some people, this can be confusing and unpleasant.
- Produce potentially serious respiratory complications
- Cannot be used for surgery on Hypotension, Bronchospasm Larynx, Pharynx & Bronchi.
- The onset of action is slower than other induction drugs.
- Generalized increase in the muscle tone and purposeful movements It produces central sympathetic stimulation, which increases, arterial blood pressure, heart rate, and cardiac output.
- Chronic use of ketamine can lead to physical and psychological dependence, making it difficult to stop using the drug.
- Depression, anxiety, and psychosis are among the mental health issues that ketamine use can cause or worsen.
- High doses or prolonged use of ketamine may have neurotoxic effects, potentially damaging brain cells and cognitive function.
- Cost effective
- Ketamine may produce bronchial secretions and increased salivation, which may need to be controlled with further steps.

Clinical Applications of Ketamine:

Acute pain management-

Acute pain usually comes on suddenly and is caused by something specific. It is sharp in quality. Acute pain usually does not last longer than six months. It goes away when there is no longer an underlying cause for the pain**.**

IV low dose ketamine (0.5 mg/kg) is devoid of any hemodynamic changes and adverse effects and is an optimal dose for pre-emptive analgesia in laparoscopic cholecystectomy. Pre-emptive intranasal ketamine1.5 mg/kg enhances postoperative analgesia after endoscopic nasal surgery. Ketamine administration has not been approved by the Food and Drug Administration (FDA) for neuraxial methods, and neurotoxicity has been observed in intrathecal continuous infusion of its racemic mixture, which, of course, appears to have occurred due to its preservative content, as no such cytotoxic effects have been observed in intrathecal administration of the preservative free type. Intranasal ketamine has a higher bioavailability than oral, and some studies have shown it to be effective in acute pain management following outpatient surgery procedures in children; psychosomatic effects have also been observed with this method.

Ketamine is a suitable analgesic for use outside the operating room, especially in emergency conditions, as it maintains cardiovascular and respiratory stability in patients, while causing potent analgesia similar to opioids, and respiratory depression. Nowadays, concomitant administration of ketamine with propofol or in a mixture called "Ketorolac" is performed in some medical centers, used to induce analgesia and sedation in some procedures (procedural sedation).

Low dose regimes (in the range of IV 0.25–0.5 mg/kg as an initial bolus followed by 50–500 μg/kg/h) have been proposed as an adjunct for postoperative analgesia and for reduction of exogenous opioid-induced hyperalgesia. A recent review of randomized double blinded clinical trials of ketamine added to opioids in IV patient-controlled

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analgesia for postoperative pain found that the ketamine-opioid combination significantly reduced pain scores, cumulative morphine consumption and postoperative desaturation in patients undergoing thoracic surgery. There are a limited number of reports that indicate the role of multimodal pain therapy including ketamine in preventing postoperative chronic pain.

Chronic pain management –

Current interest in ketamine focuses on its ability to alleviate chronic pain, especially when chronic pain has a neuropathic component. Chronic pain is discomfort that continues beyond the usual timeframe for healing, becoming classified as chronic when it persists for longer than three months.

It is a multifactorial issue, affecting roughly 20% of the world's population. Chronic pain is responsible for over 15% of patient visits and is associated with significant disruptions in the quality of life and emotional well-being. Chronic pain patients with resulting limited activity are also more likely to have comorbid conditions such as depression, COPD, and diabetes. There are many types of chronic pain, generally categorized between primary and secondary pain. Chronic primary pain cannot be explained by another condition or disease process. In contrast, other forms of chronic pain include neuropathic, musculoskeletal, cancer, postsurgical or posttraumatic, and visceral pain. Despite being a common condition, treatment for chronic pain has been challenging. Pharmacological, procedural, and behavioral interventions vary depending on chronic pain type, but many patients fail to experience a significant pain reduction. For example, randomized clinical trials (RCTs) studying pharmacotherapy in chronic neuropathic pain found that less than half of patients experience clinically significant pain relief.4 Furthermore, many chronic pain treatments have concerning adverse effects, particularly opioid.

One of the first applications of ketamine for analgesia was via intravenous infusion due to the ability to avoid first-pass metabolism and the well-controlled nature of administration. Additionally, these infusions typically occurred in inpatient settings allowing the healthcare team to monitor for adverse conditions and track treatment efficacy. The main way that ketamine acts is by inhibiting the N-methyl-D-aspartate (NMDA) receptors, which are involved in both the central sensitization process and the transmission of pain signals. Exaggerated pain responses result from central sensitization, a condition in which the nervous system becomes extremely sensitive to stimuli. Ketamine helps lessen this hypersensitivity, a defining feature of chronic pain syndromes, by inhibiting these receptors.

Ketamine interferes with the transmission of pain signals from the peripheral nervous system (CNS) to the brain. This helps to reduce pain perception and increase pain tolerance. It also has anti-inflammatory actions, which may be especially useful in chronic pain illnesses related with inflammation, such as arthritis or CRPS Ketamine as a therapy for cancer and chronic pain that is intractable to well-established therapeutics such as opioids. While ketamine has long been known as a dissociative anesthetic, its use as an analgesic agent in non- anesthetic doses is much more recent.

Chronic pain and depression are both leading causes of years lost to disability worldwide, as they are typically refractory to conventional treatments. There is considerable overlap between chronic pain and depression in terms of prevalence and treatment, with many therapies typically used to treat one being effective for the other. One such treatment that intersects with both conditions is ketamine, which has generated enormous interest among health care providers, patients and their caregivers, and patient advocacy groups. Systematic and evidence-based reviews have found ketamine to be effective for both chronic pain and depression, and recent years have witnessed a dramatic increase in research and publications, clinical use, and publicity as determined by Internet traffic. But because ketamine has been clinically available for almost 50 years, it has not been subject to the same scrutiny by the US Food and Drug Administration (FDA) or post marketing surveillance as drugs that remain on patent protection.

II. CONCLUSION

Ketamine is a special kind of aesthetic that mainly works as an NMDA receptor antagonist and has analgesic and aesthetic qualities. It causes dissociative aesthesia, which puts the patient in a trance-like state while maintaining some respiratory function, cardiovascular stability, and airway reflexes. Because of these characteristics, ketamine is especially helpful in emergency situations, trauma situations, and for people with weakened cardiovascular systems. When used as directed, it is usually safe, although there is a chance of experiencing adverse effects include emerging delirium, elevated intracranial pressure, and hallucinations. Ketamine is a useful tool in modern aesthesia because of its

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adaptability, quick onset, and capacity to produce drowsiness and analgesia, particularly in particular clinical situations when other aesthetics might not work as well. However, for its use in general anesthesia to be beneficial, close observation and control of any potential side effects are necessary.

Ketamine is a useful agent for induction of anaesthesia, procedural sedation, and analgesia. Its properties are appealing in many awkward clinical scenarios. Practitioners need to be cognizant of its side effects and limitations**.** Ketamine by virtue of some of its unique pharmacological advantages and newly found clinical properties has a wide range of clinical applications.

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