Use Of Dexmedetomidine and Ketamine for obese patients undergoing abdominal surgeries

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Abstract

Background: The World Health Organization (WHO) defines obesity as "a condition in which percentage body fat (PBF) is increased to an extent in which health and well-being are impaired, and, due to the alarming prevalence increase, declared it as a "global epidemic" Overweight and obesity were estimated to afflict nearly 1.5 billion adults worldwide in 2008 , predicted in 2030 globally an estimated 2.16 billion adults will be overweight, and 1.12 billion will be obese. Multimodal analgesia involves the use of different classes of analgesic medications (NSAIDs, COX2 inhibitors, gabapentinoids, or acetaminophen in combination with morphine IV-PCA) with different mechanisms of action on the peripheral and/or central nervous system. The different combinations of these drugs lead to additive or synergistic effects on pain relief and can potentially reduce the side effects of mono-modal interventions. Ketamine is recommended in severe pain management, and subanesthetic doses considered to have evidence of efficacy in acute pain are boluses < 0.35 mg/kg and infusions at 0.5-1 mg/kg/h, with no intensive monitoring required. Dexmedetomidine in postoperative pain for Opioid-sparing seem a promising avenue by which to improve postoperative outcomes

Keywords: Dexmedetomidine, Ketamine, obese patients

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The World Health Organization (WHO) defines obesity as "a condition in which percentage body fat (PBF) is increased to an extent in which health and well-being are impaired, and, due to the alarming prevalence increase, declared it as a "global epidemic" (**World Health Organ Tech Rep Ser.(2000)).**
Overweight and obesity were estimated to afflict nearly 1.5 billion adults worldwide in 2008 , predicted in 2030 globally an estimated 2.16 billion adults will be overweight, and 1.12 billion will be obese **(Kastorini et al. ,2011).**

Body mass index or BMI is a statistical index using a person's weight and height to provide an estimate of body fat in males and females of any age. It is calculated by taking a person's weight, in kilograms, divided by their height, in meters squared, or BMI = weight (in kg)/ height^2 (in m^2). The number generated from this equation is then the individual's BMI number. The National Institute of Health (NIH) now uses BMI to define a person as underweight, normal weight, overweight, or obese instead of traditional height vs. weight charts. **(World Health Organ Tech Rep Ser, 2000) (WHO Expert Consultation, 2004).**

In the obese patient, volumes of distribution, binding and elimination of drugs are unpredictable. This uncertainty necessitates that the anaesthetist pay more attention to the clinical end points of drug action such as loss of verbal contact, tachycardia etc. rather than focusing specifically on whether to dose on ideal, lean or actual body weight **(Adams & Murphy,2000).**

Some pharmacological certainties are a reduction in total body water, higher fat mass, relatively higher lean mass, higher Glomerular Filtration Rate(GFR) , increased renal clearance and normal hepatic clearance. The apparent volume of distribution for a fat-soluble drug such as thiopentone is increased because of the lipophilic nature and therefore the dose should be increased but a raised volume of distribution also results in reduced elimination resulting in prolonged effects **(Shankman & Shir ,1993).**

Slow emergence after use of fat-soluble volatile agents may be due to central sensitivity as much as due to delayed release from adipose stores. If available, use relatively insoluble agents as much for speed of reversal as to reduce postoperative drowsiness. The risk of halothane hepatitis may be higher in obese patients, although overall is still very low **(Shankman& Shir ,1993).**

Postoperative complications:

Post surgically, obese patients as opposed to non-obese patients possess a higher risk for experiencing respiratory complications such as acute respiratory failure and pneumonia. Lung collapse occurs more often in obese patients following extubation **(Hodgson & Murphy et al.,2015) (Carron et al., 2020).**

Patients that are non-obese may experience atelectasis post surgically; however, this condition will rapidly resolve following surgery. On the other hand, in the obese patients, atelectasis takes a longer time to resolve and may result in breathing difficulties post surgically**(Hodgson et al.,2015)**.

Postoperatively, obese patients should be closely monitored in the post anaesthesia care unit (PACU) and the following steps should be considered: the patient should be nursed with the head in an upright position **(Ogunnaike et al.,2002)(Thorell et al. ,2016)** and the use of standard oxygen therapy as well as the use of CPAP or non-invasive positive pressure ventilation (NIPPV) should be considered following extubations **(Nightingale et al.,2015)(Pelosi & Gregoretti , 2010)(O'Gara & Talmor ,2018).**

Post surgically, it is not recommended that continuous infusions be used for pain management in obese patients requiring opioids. Instead, depending on the procedure performed, opioid analgesics such as fentanyl or morphine can be used for pain control **(Carron et al.,2020).**

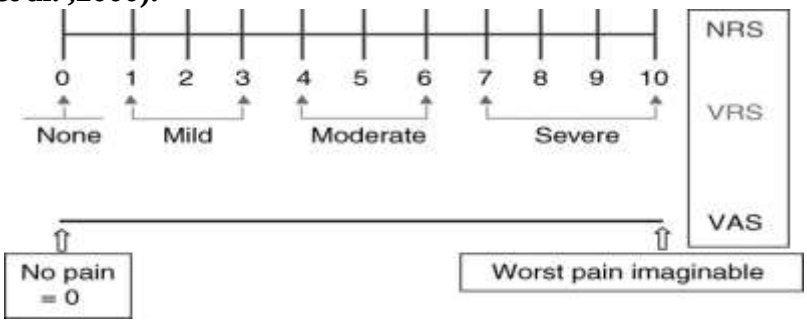
It is also important to note that myopathies such as rhabdomyolysis can occur in the obese following surgery; therefore, close monitoring is important for the development of deep tissue pains. If post surgically, signs of rhabdomyolysis occur, then steps should be taken to immediately treat this condition and prevent the occurrence of acute kidney injury (AKI) **(Wool et al,2010).**

In addition, evidence suggests that postoperative cognitive dysfunction (POCD) may be a complication observed more commonly in obese patients. Despite the fact that only a minimal association has been established between obesity and this postsurgical complication, it is important to be cognisant of this potential development **(Feinkohl et al,2016).**

Before discharge for care on the surgical ward, it is important that obese patients be monitored for a minimum time of 1 h to ensure that normal respiratory parameters are returned and maintained (**Carron et al.,2020) (Seet& Chung ,2010).**

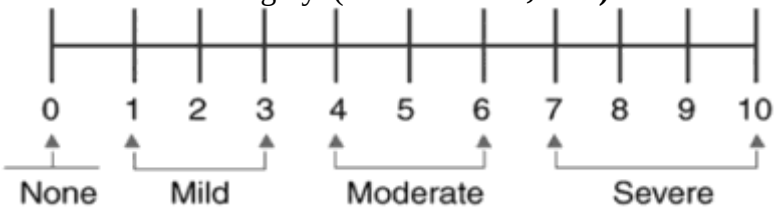
Assessment of pain can be a simple and straightforward task when dealing with acute pain and pain as a symptom of trauma or disease.

The well-known visual analogue scale (VAS) and numeric rating scale (NRS) for assessment of pain intensity agree well and are equally sensitive in assessing acute pain after surgery, and they are both superior to a four-point verbal categorical rating scale (VRS). They function best for the patient's subjective feeling of the intensity of pain right now—present pain intensity. They may be used for worst, least, or average pain over the last 24 h (**Breivik et al. ,2000).**



(figure 4.Numerical Rating score)(Breivik at al,2000)

An NRS with numbers from 0 to 10 ('no pain' to 'worst pain imaginable') is more practical than a VAS, easier to understand for most people. The NRS and the VAS have been shown to give almost identical values in the same patient at various times after surgery (**Breivik et al. ,2000).**



(figure 5.Visual Analogue scale)(Esteban et al,2019)

Perioperative pain management :

Multimodal analgesia involves the use of different classes of analgesic medications (NSAIDs, COX2 inhibitors, gabapentinoids, or acetaminophen in combination with morphine IV-PCA) with different mechanisms of action on the peripheral and/or central nervous system.

The different combinations of these drugs lead to additive or synergistic effects on pain relief and can potentially reduce the side effects of mono-modal interventions. The drugs used for this purpose include:

Acetaminophen (paracetamol): it is effective as an analgesic mainly if used in combination with NSAIDs or morphine. Its use reduces opioids use**(Hyllested et al.,2002)(McDaid et al. ,2003).**

NSAIDs: are indicated for the treatment of moderate pain when used alone. Their use in multimodal analgesia reduces morphine consumption and related side effects **(Elia et al.,2005).**

Opiates: They reduce anxiety and dyspnea **(Abernethy et al.,2003).**

Gabapentinoids such as gabapentin and pregabalin can be considered as a component in multimodal analgesia. They act by decreasing the release of neurotransmitters in the synapse, thus providing a nociceptive blocking activity **(Coccolini et al ,2022).**

Alpha-2-agonists: in addition to their anti-hypertensive effect, they have been shown to have a sympatholytic effect by inhibiting norepinephrine release, thus reducing the opiates requirements **(Coccolini et al ,2022).**

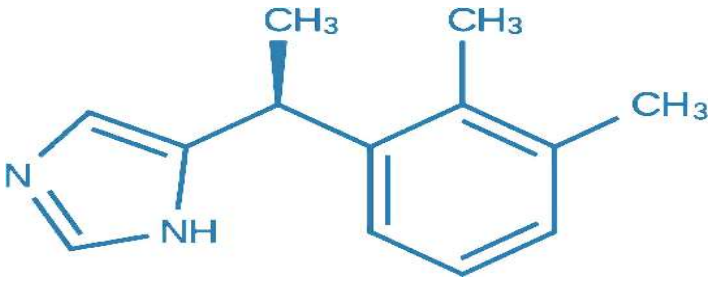
Ketamine is recommended in severe pain management, and subanesthetic doses considered to have evidence of efficacy in acute pain are boluses < 0.35 mg/kg and infusions at 0.5-1 mg/kg/h, with no intensive monitoring required **(Laskowski et al.,2011).**

Dexmedetomidine in postoperative pain for Opioid-sparing seem a promising avenue by which to improve postoperative outcomes **(Jessen et al.,2001)**

Dexmedetomidine

Chemical structure

Dexmedetomidine is a highly selective alpha 2 adrenoceptor (α2- AR) agonist that was introduced to anesthesia practice. It produces dose dependent sedation, anxiolysis and analgesia without respiratory depression. Dexmedetomidine enhances anesthesia produced by other anesthetic drugs, causes perioperative sympatholysis and decreases blood pressure by stimulating central α2 and imidazoline receptors. It is the dextrorotatory S-enatiomer of medetomidine and is chemically described as (+)-4-(2, 3- dimethyle phenyl) ethyl-1 H-imidazole monohydrochloride with molecular weight as 236.7.The empirical formula is C13H16HCl **(Barr et al., 2013).**



(Fig 7. Chemical structure of dexmedetomidine.) (kaur et al ., 2011)

Pharmacodynamics:

Dexmedetomidine is a relatively selective α2 adrenoceptor agonist with a broad range of pharmacologic properties. Alpha2-AR agonists produce clinical effects after binding to G-Protein-coupled α2-AR, of which there are three subtypes (α2A, α2B, and α2C) with each having different physiological functions and pharmacological activities. These receptor subtypes are found in the central, peripheral, and autonomic nervous system, as well as in vital organs and blood vessels **(Bekker et al., 2008).**

Dexmedetomidine is 8 to 10 times more selective towards α2-AR than clonidine. Alpha2 selectivity is observed following slow intravenous infusion of low and medium doses (10-300 mcg/kg). On the other hand both α1 and α2 activities are observed following slow intravenous infusion of high doses (>1000mcg/kg) or with rapid intravenous in animals. Sedative actions are believed to be mediated primarily by postsynaptic α2 adrenoceptors **(Bekker et al., 2008)**.

Dexmedetomidine has a low affinity for beta adrenergic, muscurinic, dopaminergic and serotonin receptors. It binds the α2 receptors of locus ceruleus and spinal cord and causes sedation and analgesia respectively. Higher affinity to α2 receptor selectively leads to vagomimetic action on the heart rate (bradycardia) and vasodilatation. Lastely the role as an antishivering agent and diuretic is yet to be established **(Bekker et al., 2008)**.

Pharmacokinetics

Absorption

Oral bioavailability is poor because of extensive first pass metabolism. However, after sublingual & intranasal administration bioavailability is high (84%), giving it a potential role in pediatric sedation and premedication. It undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine (95%), and faeces (4%)**(Bergese et al., 2010).**

Distribution

Following intravenous administration, dexmedetomidine shows rapid distribution phase with a distribution half-life of six minutes and a terminal elimination half-life (t1 /2) of approximately two hours. Dexmedetomidine exhibits linear kinetics in the range between 0.2 - 0.7 micrograms (mcg)/kg/hr. on i.v. infusion up to 24 h. In steady state, volume of distribution is about 118l and 94% is protein bound **(Bergese et al., 2010).**

Metabolism & excretion

Biotransformation involves both direct glucuronidisation (the major pathway) as well as cytochrome P450 mediated metabolism **(Bergese et al., 2010).**

In subjects with varying degree of hepatic and renal impairment, clearance is lower than in normal subjects, so, it may need dose reduction. Morever the pharmacokinetic profile of dexmedetimidine is not altered by age **(Berkenbosch et al., 2005).**

Dosage and routes of administration :

Dexmedetomidine Hydrochloride injections are available as Dexmedetomidine 50mcg/0.5ml, 100mcg/ml and 200mcg/2ml.It should be used with controlled intravenous device when being used via intravenous route. The dose should be individualized and titrated to the desired clinical effect. Dose reduction is necessary in elderly patients or those with impaired hepatic or renal function **(Paramus, 2016).**

Route	**Dosage**

Intravenous	Loading dose of 1 mcg/kg over 10-20 minutes followed by a maintenance infusion in the range of 0.2- 0.7mcg/kg/hr. The rate of infusion can be increased in increments of 0.1mcg/kg/hr or higher
Intramuscular	IM injection (2.5 mcg/kg) of dexmedetomidine has been used for premedication.
Spinal	0.1-0.2 mcg/kg
Epidural	1-2mcg/kg
Peripheral nerve block	1mcg/kg
Buccal	1-2 mcg/kg
Intranasal	1-2 mcg/kg

(Table4.Dosage and routes of administration of dexmedetomidine) (Ebert et al., 2000).

Adverse effects

The most frequently observed adverse effects include hypotension, hypertension, bradycardia, dry mouth and nausea. Other reported adverse effects include fever, rigors, cyanosis and muscle weakness. It may also lead to arrhythmias, AV Block, cardiac arrest, T-wave inversion, tachycardia, angina pectoris, pulmonary edema, bronchospasm, respiratory depression, syncope, neuropathy, paresthesia, paresis, hyperklaemia, lactic acidosis and hyperglycemia. Tolerability of dexmedetomidine hydrochloride was noted in healthy subjects who achieved plasma concentrations from 1.8 up to 13 times the upper boundary of the therapeutic range. The most notable effect observed in those who achieved the highest plasma concentration was AV block which is resolved spontaneously within one minute **(Arian and Ebert, 2002).**

Drug interaction

Vitro studies indicated that clinically relevant cytochrome P 450 mediated drug interactions are unlikely. Co-administration of anesthetics, sedatives, hypnotics or opioids with dexmedetomidine hydrochloride are likely to lead to an enhancement of their effects. Hence, a reduction in dosage with these agents is required. Additionally, in situations where other vasodilators or negative chronotropic agents are used, coadministration of dexmedetomidine could have an additive pharmacodynamic effect and should be administered with caution and careful titration **(Gerlach and Dasta, 2007).**

Clinical applications

Premedication

As it is a sedative, anxiolytic, analgesic, sympatholytic, and has stable hemodynamics, dexmedetomidine is used in premedication. It decreases oxygen consumption in the intraoperative (upto 8%) and postoperative period (up to 17%) **(El-Tahan et al., 2012).**

In obese patients

The excellent safety of dexmedetomidine in patients with sleep-disordered breathing SDB and OSA has led to its current popularity and widespread use in bariatric anesthesia. Dexmedetomidine significantly reduces opioid consumption and Postoperative nausea & vomiting PONV in patients undergoing bariatric surgery, with earlier discharge from the recovery room and the hospital.

This significantly reduce the otherwise frequent and sometimes problematic bradycardia, which has the potential to progress rapidly to asystole and cardiac arrest. Additional benefits of intraoperative dexmedetomidine include reductions in emergence phenomena and shivering in the PACU **(Ziemann et al. ,2014).**

Post-operative analgesia

Dexmedetomidine also provides intense analgesia during the postoperative period, as in a study, it was considered that the analgesic requirements were reduced by 50% in cardiac patients and the need for rescue midazolam for sedation was diminished by 80% **(Barr et al., 2013).**

Procedural sedation

Dexmedetomidine is indicated for sedation of non intubated patients prior to and/or during surgical and other procedures. It has been safely used in transesophageal echocardiography, colonoscopy, awake carotid endarterectomy, and shockwave lithotripsy **(Gerlach et al., 2007),**

morever vitreoretinal surgery, and pediatric patients undergoing tonsillectomy. The usual dose of dexmedetomidine for procedural sedation is 1 mcg/ kg, followed by an infusion of 0.2 mcg/kg/h. Its onset of action is less than 5 min and the peak effect occurs within 15 min. Dexmedetomidine provides a titratable form of hypnotic sedation that can be easily reversed by the α2-AR antagonist atipamezole **(Scheinin et al ,1998).**

As an adjuvant in local and regional techniques

The highly lipophilic nature of dexmedetomidine allows for its rapid absorption into the cerebrospinal fluid and binding to α2-AR of the spinal cord for its analgesic action. It prolongs the duration of both sensory and motor blockade induced by local anesthetics irrespective of the route of administration (e.g., epidural, caudal, or spinal) **(Piccioni and Fanzio, 2008).**

Intraarticular use

Intraarticular dexmedetomidine in patients undergoing arthroscopic knee surgery was showen to improve the quality and duration of postoperative analgesia (**Barr et al., 2013).**

Controlled hypotension

Indeed, dexmedetomidine is an effective and safe agent for controlled hypotension mediated by its central and peripheral sympatholytic action. Attenuation the response to tracheal intubation and extubation: By its sympatholytic property, at IV doses of 0.33 to 0.67 µg/kg given 15 min before surgery defentely attenuate the hemodynamic response to endotracheal intubation **(Venn et al., 2002).**

Awake Intubation

Dexmedetomidine is also used for securing the airway with fiberoptic intubation **(Bergese et al., 2010).**

Anaesthetic sparing effect

When used intraoperatively in lower concentration, it was shown that the requirement for the other anaesthetic agents is reduced **(Barr et al., 2013)**

Cardiovascular stabilizing effect

Studies have demonstrated the potential therapeutic applications of dexmedetomidine in the treatment of arrhythmias. Additionally, its use during cardiac surgery has been associated with a decreased incidence of postoperative ventricular and supraventricular tachyarrhythmias. Morever, dexmedetomidine may be useful for the treatment of the deleterious cardiovascular effects of acute cocaine intoxication and overdose **(Shehabi et al., 2004).**

Neurosurgery

In addition to dexmedetomidine hemodynamic stability, it attenuates neurocognitive impairment (delirium and agitation) allowing immediate postoperative neurological evaluation. It does not interfere with neurological monitors, and has an upcoming role in neurosurgery **(Piccioni and Fanzio, 2008)**.

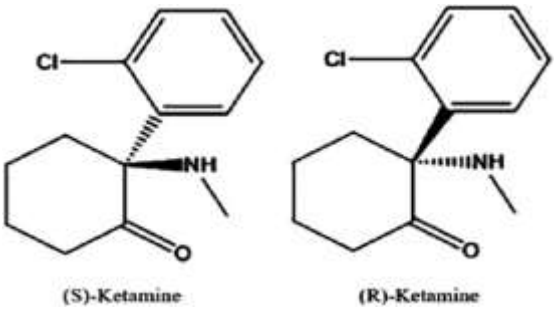
Ketamine

Chemical structure of ketamine

Ketamine is a phenylcyclohexylamine derivative consisting of its two optical enantiomers, (S)- and (R)-forms. It became commercially available for human use in 1970 as a rapid-acting i.v. anesthetic. Ketamine was derived from phencyclidine (PCP) with the aim of lessening the serious psychotomimetic/psychodysleptic side effects **(Zanos et al., 2016).**

Despite these side effects, ketamine has proven to be a desirable drug due to its short half-life and lack of clinically significant respiratory depression. In addition to its well-characterized anesthetic action in adults,

children, and obstetric patients, ketamine possesses an analgesic, anti-inflammatory effects, and antidepressant features **(Zanos et al., 2016).**



(Figure 8.) chemical structure of ketamine. (sinner & Graf 2008)

Pharmacokinetics

Absorption

Bioavailability following an intramuscular dose is 93%, an intranasal dose 25%–50%, an oral dose only 17% **(Larenza et al. 2007).**

Distribution

Ketamine is rapidly distributed into the brain and other highly perfused tissues; 12% are protein-bound in the plasma. Therefore oral administration produces lower peak concentrations of ketamine, but increased amounts of the metabolites norketamine and dehydro-norketamine **(Larenza et al. 2007).**

Metabolism & execretion

Ketamine undergoes extensive metabolism, initially via nitrogen demethylation to norketamine, a reaction that is catalyzed primarily by the cytochrome P450 liver enzymes CYP2B6 and CYP3A4 **(Portmann et al., 2010).**

In adult humans, ketamine has a high rate of clearance and a short elimination half-life of 2–4 hours **(Domino, 2010).**

However, there is evidence that repeated administration of ketamine prolongs its elimination time. For example, as in a study, it was shown that among three instances of single i.v. infusions of ketamine (doses ranged from 0.75 to 1.59 mg/kg), the elimination of ketamine was slowed from 2 days following the first infusion to 5 days after the second, and 11 days following the third. Elimination of norketamine remained constant (i.e., 5 days after each infusion **(Adamowicz and Kala, 2005).**

Overall, it is important to note that there are important species differences in regard of half-life values and clearance rates of ketamine, and its metabolites. This should be taken into consideration when comparing the behavioral actions of specific dose regimens for ketamine and its metabolites in mice, rats, and humans. Nevertheless, the brain levels of ketamine and its metabolites following administration of ketamine in humans are not known, and, therefore, direct comparisons are not straight forward **(Zanos et al., 2016).**

Pharmacodynamics

Ketamine is a N-methyl-D-aspartate (NMDAR) antagonist, and ketamine's well-characterized analgesic and anesthetic effects are primarily attributed to NMDAR inhibition. However, ketamine's pharmacological targets are not limited to NMDARs, as it has been reported that ketamine interacts with several other receptors and ion channels, including dopamine, serotonin, sigma, opioid, and cholinergic receptors, as well as hyperpolarization-activated cyclic nucleotidegated (HCN) channels, However, ketamine typically has a lower affinity (higher inhibitory constant—Ki—values) for these receptors and channels compared with NMDARs, and independent laboratories have not validated many of the reported findings **(Franks and Lieb, 1994).**

Early pharmacodynamic studies of (R,S)-ketamine were conducted in rats and examined the anesthetic effects of the parent compound and its two principal metabolites, (R,S)-norketamine and (2R,6R;2S,6S)-HNK. The results demonstrated that a 40mg/kg i.v. bolus administration of (R,S)-ketamine and (R,S)-norketamine produced anesthetic actions and increased spontaneous locomotor activity during the postanesthetic recovery phase, whereas (2R,6R;2S,6S)-HNK (in the same dose) had no anesthetic or hyperlocomotor effects **(Leung and Baillie, 1986).**

N-Methyl-D-Aspartate Receptors:

Historically, the primary recognized receptor target of ketamine is the NMDAR, in which ketamine acts as a noncompetitive open-channel blocker **(MacDonald et al., 1987).**

NMDARs are glutamatergic ion channels made of different combinations of four subunits encoded by one of seven genes: GluN1, GluN2A–D, andGluN3A–B **(Vyklicky et al., 2014).**

NMDARs are highly permeable to calciumions, which can trigger the activation of a number of intracellular pathways in neurons and glial cells. At resting state, NMDAR channels are tonically blocked by magnesium (Mg^{2+}). Efficient receptor activation requires the following: 1) membrane depolarization, which displaces the Mg^{2+} block, and 2) binding of both glutamate and the coactivator glycine and/or D-serine **(Paoletti et al., 2013).**

In addition to a possible role in the anesthetic properties of ketamine, HCN1 channel inhibition may have a role in ketamine's antidepressant actions because reduced HCN1 activity in the hippocampus has been associated with antidepressant effects in rodents **(Han et al., 2017).**

Dosage

The therapeutic range of ketamine or S(+)-ketamine makes them one of the safest sedative agents for most emergency clinical and preclinical situations. Distinct and useful effects are obtained when the drugs are administered at different doses. Lowdose ketamine infusion provides potent analgesia, which is useful in conjunction with sedation or as a narcotic in areas with scarce resources **(Sinner & Graf ,2008).**

Racemic Ketamine Intravenously administered, the induction dose for general anaesthesia is 1–2 mg/kg; after induction, a continuous dose of 1–6 mg/kg per hour is necessary. In lower concentrations of 0.25–0.5 mg/kg an adequate analgesia can be seen. The same concentration is necessary for sedation, whereby a permanent dose of 0.4–1 mg/kg per hour is required for continuous sedation. To get the same effects by intramuscular injections 2–4 times higher doses have to be injected. Higher doses are also necessary for rectal (8–10 mg/kg) and nasal admission (5 mg/kg) **(Sinner& Graf .2008).**

Clinical Therapeutic Effects:

1. Anesthetic:

Ketamine induces general, dissociative anesthesia in humans **(Domino, 2010).** Moreover, ketamine is also used as an adjunct to local anesthetics in veterinary practice and in humans **(Kathirvel et al., 2000)**. The average steady-state plasma concentration necessary to achieve anesthesia with ketamine was reported to be 2200 ng/ml, or 9.3 mM. Oral (500 mg) or intrarectal (8–15 mg/kg) administration of ketamine are sufficient to induce sedation and/or general anesthesia in humans **(Craven, 2007).**

2. Analgesic:

An early report of the analgesic effects of ketamine was provided by Weisman (1971), who observed these effects in pediatric ophthalmologic procedures. Ketamine is described to provide a form of analgesia quantitatively and qualitatively similar to opioids, but with less respiratory depressive effects, as was reported in pediatric patients treated for fractures, burns or in cases of traumatic amputation. When administered i.v. or i.m., ketamine's analgesic effects are associated with plasma concentrations ranging between 70 and 160 ng/ml, or approximately 0.29–0.67 mM **(Mc Guinness et al., 2011).** Intravenous ketamine is used as an analgesic to reduce chronic and acute postoperative pain **(Laskowski et al., 2011).**

3. Antidepressant:

Evidence of ketamine's antidepressant actions dates back to the 1970s. In preclinical studies, ketamine was found to exert effects similar to those observed following administration of classic antidepressant drugs (i.e., tricyclic antidepressants and monoamine oxidase inhibitors) in rodents, in particular, oral administration of ketamine to mice reversed reserpine-induced hyperthermia at the dose of 40mg/kg and prevented tetrabenazine induced ptosis with an ED50 of 27.6 mg/kg **(Sofia and Harakal, 1975)**, which are phenotypes reversed by classical antidepressants **(Delini-Stula, 1980)**. Additional studies have shown that ketamine reduces suicidal ideation and decreases anhedonia in patients suffering from major depression **(Ballard et al., 2017)**.

4. Anti-Inflammatory:

Inflammation is a critical homeostatic mechanism used by the body to fight infections and to heal tissue injuries. Inflammatory reactions are triggered once immune cells of the immune system become activated, whether by invading pathogens or tissue damage. Release of proinflammatory cytokines by these cells then activate members of the adaptive immune system to initiate an inflammatory response **(Newton and Dixit, 2012).** In addition to its effects on the proinflammatory cytokines, ketamine dose dependently reduces inflammation-induced nitric oxide production. The anti-inflammatory effects of ketamine have been observed when the drug was administered prior to, and following an immune stimulation, indicating that it may be able to prevent exacerbation of inflammation, and also reduce existing inflammation **(Loix et al., 2011).**

Adverse effects

1. Psychoactive Effects:

a. Dissociative and psychotomimetic effects: Ketamine dose dependently exerts broad influences on consciousness and perception, with some patients reporting dissociative and extracorporeal sensations (out-of-body experiences/illusions) when recovering from ketamine-induced anesthesia. Whereas, these effects of ketamine established the drug as a dissociative anesthetic, the same effects have been noted following subanesthetic doses as well **(Krystal et al., 1994)**.

The most common psychoactive effects reported after a single subanesthetic i.v. administration of ketamine include dissociation (distortions in visual, auditory, or somatosensory stimuli, or alterations in the perception of self or time), positive psychotomimetic effects (conceptual, disorganization, hallucinations, suspiciousness and unusual thought content), and negative psychotomimetic effects (blunted affect, emotional withdrawal, motor retardation) **(Li et al., 2016).**

b. Memory and cognitive impairment:

In addition to the dissociative and psychotomimetic symptoms, several studies have identified unfavorable effects of subanesthetic administration of ketamine on cognition **(Ke et al., 2018).** Studies have reported that ketamine decreases mental sharpness, concentration, recall and recognition, as well as explicit (episodic and semantic) and implicit (procedural) forms of memory **(Driesen et al., 2013).**

c. Abuse:.

Whereas the acute psychotropic effects of ketamine may cause discomfort for some individuals, its dissociative properties have made it desirable for recreational use. However, some users may experience increased agitation or anxiety/panic attacks. Within 10 minutes following initiation of a 40-minute i.v. infusion of a subanesthetic dose of 0.5 mg/kg ketamine (resulting in plasma Cmax estimated to be ;100–250 ng/ml or 0.42–1.1 mM), healthy subjects reported feelings of being "high" (i.e., subjectively comparable to that of alcohol intoxication **(Arditti et al., 2002).**

2. Direct and Indirect Peripheral Effects:

At subanesthetic doses of ketamine (;0.5 mg/kg administered i.v. over 40 minutes), it can lead to vestibular perturbations, including dizziness and nausea/ vomiting. Ketamine's actions on the sympathetic nervous system are associated with broad cardiovascular outcomes (e.g.,tachycardia, hypertension, palpitations) evident in both clinical (0.5–1.0 mg/kg i.v) and recreational settings (100–200 mg i.m. or s.c.) **(Murrough et al., 2013).** Although generally considered clinically insignificant, mild respiratory depression is reported at doses ranging from 0.39 to 3.0 mg/kg. Additionally, hemodynamic effects (i.e., arterial pressure and heart rate) have not been found to vary significantly among (S)-, (R)-, and (R,S)-ketamine, although at least one

study suggests that (S)- ketamine specifically contributes to (R,S)-ketamine's cardiovascular effects, such as increased blood pressure. Overall,a recent retrospective analysis in individuals who received i.v. ketamine infusions (0.5 mg/kg over 40 minutes) reported that alterations in blood pressure were modest, well tolerated, and clinically insignificant **(Riva et al., 2018).** Also, ocular effects (e.g., nystagmus, diplopia, dilation) are reported in recreational contexts **(Weiner et al., 2000).**

3. Neurotoxicity:

With emerging indications requiring repeated ketamine administration (e.g., antidepressant actions), there are concerns of more profound untoward effects of treatment, including the induction of Olney lesions. First reported in 1989, Olney lesions are characterized by vacuoles occurring in the cytoplasmic compartment of selected neuronal populations, where lysis of mitochondria was reported **(Olney et al., 1991).**

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