KETAMINE
A new look at an old drug

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## CONTENTS

**INTRODUCTION** ........................................................................................................ 3  
Chemistry ................................................................................................................ 4  
Metabolism .............................................................................................................. 5  
**PHARMACODYNAMICS** ............................................................................................ 6  
**USES OF KETAMINE** .............................................................................................. 10  
Induction and Maintenance of General Anesthesia in Emergency ......................... 10  
Preoperative Sedation / Analgesia (PSA).................................................................... 14  
Ketamine and Midazolame .................................................................................... 16  
Ketamine and Propofol (Ketofol) ........................................................................... 16  
Ketamine and Nitrous Oxide .................................................................................. 18  
Guideline for Ketamine sedation of children in Emergency Departments ............. 18  
**KETAMINE IN CHRONIC PAIN MANAGEMENT** ..................................................... 19  
Physiology of pain ..................................................................................................... 19  
Oral Ketamine in treatment of Chronic Pain .......................................................... 22  
Ketamine as an adjuvant to Neuraxial Block ............................................................ 23  
Prehospital use of Ketamine .................................................................................. 23  
Ketamine in Labour Pain .......................................................................................... 24  
Ketamine and Opioid Tolerance ............................................................................. 24  
Management of Opioid Tolerance ........................................................................... 24  
Ketamine in Head Injury ........................................................................................ 26  
Conclusions: Ketamine for Traumatic Brain Injury ................................................. 28  
Ketamine as Antidepressant .................................................................................... 28  
**CONCLUSION** ................................................................................................... 30  
**REFERENCES** .................................................................................................. 31
INTRODUCTION

Ketamine, a phencyclidine derivative, is arguably our most ideal anesthetic agent!

History

1958: phencyclidine (phenyl cyclohexyl piperidine, PCP) introduced into clinical anesthesia. Phencyclidine produced an unacceptably high incidence of hallucinations, confusion and delirium, so its development for use in human anesthesia was discontinued. It became commercially available for use as a veterinary anesthetic in the 1960s under the trade name of Sernylan and was placed in Schedule III under the U.S. Federal Controlled Substances regulations.

1978: due to considerable abuse phencyclidine was transferred to Schedule II under the CSA and manufacturing of Sernylan was discontinued.

1959: cyclohexamine was tried but was found to be worse than PCP (similar adverse psychotomimetic effects with less analgesia)

1962: ketamine (Ketalar) synthesized by Stevens

1965: ketamine trialed in humans and chosen as most promising from 200 PCP derivatives tested in animals

1970: ketamine officially released for clinical use in U.S.

1999: ketamine reclassified to schedule III in the US
Chemistry

Ketamine is 2-(o-chlorophenyl)-2-(methylamino) cyclohexanone (hydrochloride) Ketamine has a chiral center and is presently marketed as the racemic mixture of its two (mirror-image) enantiomers or enantiomorphs

![S-(+)-ketamine](image1.png) ![R-(-)-ketamine](image2.png)

Ketamine, molecular weight 238, is partially water soluble at pH 7.4 (pKa 7.5), and 5 to 10 times more lipid soluble than thiopental. The commercial preparation (Ketalar) is a racemic mixture of (SR)-ketamine in NaCl solution with pH 3.5 to 5.5 and is prepared in three concentrations of ketamine: 10, 50 and 100 mg/ml, with benzethonium chloride added as a preservative.

<table>
<thead>
<tr>
<th>Table I Pharmacokinetics of ketamine²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of distribution</td>
</tr>
<tr>
<td>Onset of action (i.v.)</td>
</tr>
<tr>
<td>Bioavailability</td>
</tr>
<tr>
<td>i.m.</td>
</tr>
<tr>
<td>intranasal</td>
</tr>
<tr>
<td>oral</td>
</tr>
<tr>
<td>Protein binding</td>
</tr>
<tr>
<td>Distribution half life</td>
</tr>
<tr>
<td>Elimination half life</td>
</tr>
<tr>
<td>Site of metabolism</td>
</tr>
<tr>
<td>Metabolites</td>
</tr>
</tbody>
</table>

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Metabolism

• Norketamine, with 20-30% of the activity of ketamine, is hydroxlylated to hydruxynorketamine (inactive) conjugated with glucuronate (inactive) and excreted in the urine. Norketamine, with elimination t1/2 of 6 hours, probably contributes significantly to analgesia. Plasma disappearance fits a 2-compartment model
  • t1/2(distribution) = 11 - 16 minutes.
  • Vdss = 3 L/kg (very lipid soluble)
  • clearance (Cl) = 12 - 17 ml/kg/min
  • t1/2(elimination) = 2 - 3 hours

Plasma levels needed for hypnosis and amnesia during surgery are approximately 0.7 to 2.2 mcg/ml (perhaps up to 4.0 mcg/ml in children). Awakening occurs below 0.5 mcg/ml
PHARMACODYNAMICS

1. Central Nervous System
   • Unconsciousness “dissociative anesthesia”
   • Cataleptic appearance (1 000 yard stare)
   • Eyes may remain open
   • Reflexes remain intact (corneal, cough and gag)
   • Amnesia for long term memory due to effects on hippocampal NMDA receptors synergistic with benzodiazepines
   • Onset < 30 seconds
   • Maximum effect: 1 minute after IV injection
   • Pupillary dilation and nystagmus
   • Lacrimation and salivation are common
   • Skeletal muscle tone may increase
   • Coordinated but purposeless movements
   • Good correlation between blood concentration and CNS effects
   • A plasma level of 0.6-2 mcg/ml provides general anesthesia in adults
   • A plasma level of 0.8-4 mcg/ml is required for general anaesthesia in children.
   • A single bolus of 2mg/kg provides 10-15 minutes of anesthesia with full orientation in 15-30 minutes

2. S enantiomer
   • Lower dose requirement
   • 10% faster hepatic biotransformation
   • Faster recovery
   • Analgesia occurs at concentrations above 0.1 mcg/ml (subanaesthetic concentrations of ketamine provide profound post-op analgesia)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of the effects of S-(+)- and R-(−)-ketamine (ratios)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>S(+)</td>
</tr>
<tr>
<td>NMDA affinity</td>
<td>4</td>
</tr>
<tr>
<td>Plasma concentration</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral concentration</td>
<td>1</td>
</tr>
<tr>
<td>Elimination rate</td>
<td>1</td>
</tr>
<tr>
<td>Anaesthetic potency</td>
<td>3</td>
</tr>
<tr>
<td>Side-effects</td>
<td>Similar to racemic mixture</td>
</tr>
</tbody>
</table>

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3. Cerebral Functional
   • decreased function of cortical association areas and thalamus
   • increased function of parts of limbic system, including hippocampal memory
   • decreased transmission in medial medullary reticular formation (affective-emotional component of nociception from the spinal cord to the brain)
   • a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist
   • inhibits activation of NMDA receptor by glutamate (excitatory neurotransmitter)

4. CNS Neurotransmitter
   • reduces presynaptic release of glutamate
   • potentiates effects of gamma-aminobutyric acid (GABA, inhibitory neurotransmitter) may mediate general anesthetic effect) this may explain part of the analgesic effect
   • could be responsible for elements of the "near death experience" (NDE) sometimes described.

5. Opiate Receptors
   • ketamine occupies mu and kappa opiate receptors in brain and spinal cord.
   • S-(+)-ketamine has been reported to have mu opioid receptor activity which may explain some of analgesic effect.
   • increases cerebral metabolism.
   • generalized EEG theta activity, signals analgesic activity.
   • petit mal seizure-like activity – hippocampus.
   • Increases CBF, thiopental or diazepam block the increases in CBF
   • Does not increase ICP if normocarbia is maintained. In the clinical setting, level II evidence indicates that ketamine does not increase intracranial pressure when used under conditions of controlled ventilation, co administration of a gamma-aminobutyric acid (GABA) receptor agonist, and without nitrous oxide.
   Ketamine may thus safely be used in neurologically impaired patients.

Compared with other anesthetics or sedatives, level II and III evidence indicates that hemodynamic stimulation induced by ketamine may improve cerebral perfusion; this could make the drug a preferred choice in sedative regimes after brain injury.

Ketamine does not trigger seizure activity; in fact, it much more likely prevents seizure activity by NMDA receptor antagonism.
The preponderance of evidence favors a neuroprotective action of ketamine. It seems confirmed that ketamine does not increase ICP when blood pressure is controlled and mild hypoca pnea is achieved. Kohrs 1998. Eight patients with traumatic brain injury were studied. In all patients, ICP monitoring was instituted before the study.

Ketamine, in all three doses studied (1.5, 3, and 5 mg/kg) was associated with a significant decrease in ICP (mean +/- SD: 2 +/- 0.5 mmHg [P < 0.05], 4 +/- 1 mmHg [P < 0.05], and 5 +/- 2 mmHg [P < 0.05]) among the study patients regardless of the ketamine dose used.

A Albanese 1997 Anterior fontanel pressure decreased 11% during isoflurane administration, 9% during halothane administration, 10% after fentanyl, and 10% after ketamine. These changes were statistically significant, but clinically mild, and AFP(anterior frontal pressure) remained within the normal range. Friesen 1987 Cerebrovascular CO2 response remains intact after ketamine administration reducing PaCO2 attenuates any rise in ICP caused by ketamine.

Other effect

Psychological effects "emergence reactions"
- vivid dreaming
- extracorporeal (floating "out-of-body") experience
- misperceptions, misinterpretations, illusions
- may be associated with euphoria, excitement, confusion, fear
- occur from 1 to several hours post-operative
- adults > children and women > men it is dose-related
- best attenuated or eliminated with benzodiazepines and, probably, propofol,
- may be ameliorated by prior "preemptive" positive suggestion

6. Respiratory System
- Ketamine has generally beneficial effects on the respiratory system with no more than minimal respiratory depression
- ventilatory response to CO2 unaltered
- apnea is rare and only at high doses >5mg/kg IV
- no significant change in Arterial Blood Gas analysis
- bronchodilation: bronchial smooth muscle relaxation proven in isolated bronchial muscle studies.
- increased salivation
- Airway reflexes such as cough, sneeze, and gag remain intact
7. **Cardiovascular System**

- Ketamine stimulates the cardiovascular system
- blood pressure increases
- heart rate increases, cardiac output increases, MVO2 and work increases (associated with appropriately increased coronary artery dilation and flow) relatively unrelated to dose (0.5 mg/kg = 1.5 mg/kg)
- increases central sympathetic outflow.
- increases sympathoneuronal norepinephrine release (may block this effect with barbiturates, benzodiazepines, droperidol)
- inhibits catecholamine reuptake
- in vitro: direct negative inotropic effect on isolated myocardium
- tachycardia and hypertension reduced by prior benzodiazepine
- in congenital heart disease, usually no significant change in shunt (Rt-Lt) and also no significant change in SPO2.
- Ketamine causes some increase in pulmonary artery pressure subsequently, pulmonary vascular resistance may increase more than systemic vascular resistance.
- Ketamine is an intrinsic cardiovascular suppressant. Stimulant effects are derived from release of endogenous catecholamines with catecholamine depletion depressive effects are seen.

8. **Others**

Ketamine suppresses neutrophil production of inflammatory mediators, improving blood flow and reduces migration of leukocytes through endothelia also suppresses proinflammatory cytokine production in whole blood. Ketamine inhibits activity of hepatic microsomal enzymes, CYP 2D1 and CYP3A, by 10-20%
USES OF KETAMINE

Induction and Maintenance of General Anesthesia in Emergency

I. Poor risk ASA IV (or V) patients with respiratory or cardiovascular disease (not CAD), especially reactive airway disease or hemodynamic compromise based on hypovolemia or intrinsic myocardial disease (not CAD)

ii. Rapid-sequence induction in otherwise healthy trauma victims after significant hemorrhage.

iii. Patients with septic shock

The ‘ideal’ emergency anaesthetic induction agent is one which rapidly achieves unconsciousness and yet does not itself cause haemodynamic compromise.

It may be argued that in certain circumstances, an induction of anaesthesia is too hazardous. The obtunded patient is assumed to be sufficiently unconscious to allow surgery to progress without the need for any anaesthetic agent (with the attendant side-effects). However, in practice emergency (and cardiac) anaesthesia are well documented to be associated with an increased incidence of awareness.

Ketamine induction followed by appropriate maintenance with a volatile agent yielded awareness under anaesthesia in 11% of trauma case (itself a high incidence), compared with 43% recall where no anaesthetic agent was administered (which is extremely high)(2,3)

<table>
<thead>
<tr>
<th>Intravenous induction agent</th>
<th>Effector site equilibration and ( t_{1/2\beta} )</th>
<th>Haemodynamic effects in vivo</th>
<th>Comments and idiosyncratic reactions (see text)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>Undetermined (see text), but probably (~2 \text{ min})</td>
<td>TCO, THR, IABP</td>
<td>→ or ↑CPP and ↓ICP with standard anaesthetic management</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>1.5 min</td>
<td>THR, →CO, IABP</td>
<td>Haemodynamically compromised patients unlikely to tolerate induction dose &gt; 3 mg.kg(^{-1})</td>
</tr>
<tr>
<td>Propofol</td>
<td>≤20 min</td>
<td>→HR, ↓CO, IABP, ↓inotrope, ↓vasodilatation</td>
<td>Haemodynamic compromise marked in elderly, ASA 3 or more or hypovolemic patients with ‘standard’ induction dose</td>
</tr>
<tr>
<td>Etomidate</td>
<td>~2.5 min</td>
<td>→CO, →IABP</td>
<td>Prolonged inhibition of steroid synthesis in the critically ill, withdrawn from number of countries</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>~9 min (e.g. lorazepam)</td>
<td>→CO, →HR</td>
<td>Induction time of anaesthesia incompatible with RSI</td>
</tr>
<tr>
<td>Phenylpiperidines</td>
<td>~6 min (e.g. fentanyl)</td>
<td>Vagotonic, ICO, THR, IABP, ↓inotrope, ↓vasodilatation</td>
<td>Persistent vagally mediated bradycardia can compound effects of hypovolaemia</td>
</tr>
</tbody>
</table>

CO, cardiac output; A8P, arterial blood pressure; HR, heart rate; CPP, cerebral perfusion pressure; ICP, intracranial pressure.

ASA, American Society of Anesthesiologists preoperative grade.

Increased: →, decreased: ↓, unaffected.
The clinical use of ketamine in > 10 000 articles retrieved, only the 12 studies quoted make meaningful comment(with supporting evidence) on the use of ketamine in RSI in situations of haemodynamic compromise, and only two of these directly compared ketamine with another agent. In emergency surgical patients ketamine increased mean arterial pressure by a mean of 10% it was concluded that it thus offers an advantage over thiopental in situations where hemodynamic stability is crucial. In obstetric modified rapid sequence induction (MRSI) (with rocuronium as neuromuscular blocker), ketamine enabled earlier and easier tracheal intubation than thiopentone [5].

In addition, despite its cardiovascular stability, etomidate withdrawn from a number of countries because of its prolonged inhibition of endogenous corticosteroids in critically ill patient (60% of patient) in particular patient with sepsis.

Rajeshs Sehdev et al (Ketamine for rapid sequence induction in patients with head Injury in the emergency department 2006-18, 37-44 EMA), using a literature review, he examined the evidence regarding the use of ketamine for induction of anaesthesia in patient of head injury in emergency department, he concluded, that
ketamine is a suitable drug for induction, especially in patients of potential cardiovascular instability. In addition, ketamine may be useful addition to the treatment modalities of head injury due to its pharmacological properties, haemodynamic effect and cellular pathophysiology in head injury in particular the role of NMDA receptor blockade and neurotransmitter surge. Also he concluded that avoiding ketamine use in head injury is conflicting and inconclusive.

The current objective evidence based on clinical trials is in favour of ketamine. It is notable that a number of organisations involved in delivering care to victims of trauma, especially in the developing world (International Committee of the Red Cross and the Finnish Red Cross) advocate ketamine anaesthesia for both induction and maintenance during surgery in field hospitals and recommend ketamine as a first-line agent for anaesthetic induction.

The West Midlands Ambulance Service and British Association for Immediate Care recommend ketamine for non-physician pre-hospital procedural sedation and anaesthesia, the Italian Comitato Collaborazione Medica advocate ketamine for emergency anaesthesia in field hospitals, and the Motorcycle Union of Ireland Medical Team (MUIMT) use only ketamine for pre-hospital trauma RSI. All advocate the use of ketamine for prehospital procedural sedation. The Association of Anaesthetists of Great Britain and Ireland commissioned a special ‘developing world’ supplement to Anaesthesia, in which ketamine featured as the key induction agent.

In cardiac tamponade and restrictive pericarditis ketamine maintains heart rate and filling pressures. Ketamine is also useful in congenital heart disease, especially with propensity for R -> L shunt. Ketamine is a suitable agent in malignant hyperthermia susceptible patients. Ketamine is a suitable drug for patients with large anterior mediastinal masses, when spontaneous ventilation is required during induction and intubation.

In cardiac anesthesia for correction of valvular or ischemic heart disease, using ketamine plus diazepam or midazolam as well as sufentanil by continuous infusion, has minimal hemodynamic pertubations and only transient increase in blood pressure (16)
Indications

Aged and poor risk patients
- Shock and cardiovascular instability.
- Severe dehydration.
- Respiratory failure or bronchospasm.
- Severe anaemia.
- Major thoracoabdominal procedures.
- Cardiac tamponade and constrictive pericarditis.

Obstetric patients
- Rapid sequence induction
  - Severe hypovolaemia.
  - Acute haemorrhage.
  - Acute bronchospasm.
- Low dose for analgesia
  - Supplement regional technique.
  - Transient analgesia at the time of delivery.

Adjunct to local or regional anaesthesia
- Low dose for sedation and analgesia during the procedure.
- Supplement for inadequate block.

Outpatient surgery
- Pediatric anaesthesia
  - Diagnostic and therapeutic procedures.
  - Induction of anaesthesia.
  - Caudal analgesia.
- Adult anaesthesia
  - Brief surgical procedures.
  - Supplement local or regional technique.
  - Diagnostic and therapeutic procedures.

Reactive airway disease
- Intractable bronchial asthma.
- COPD with bronchospasm.

Patients with thermal injuries
- Debridement and skin grafting.
- Dressing changes.

Postoperative analgesia
- As an adjunct with morphine PCA.
- Recovery room.

Intensive care units.

Procedural sedation in intensive care
- Pediatric cannulation, central lines.
- Adult central lines, endoscopies, dressing changes.

Developing countries and field hospitals

Chronic pain
- For patients in whom airway management may be difficult
  - Unstable cervical spine.
  - Trapped casualties.

Contra indications
- A high predisposition to laryngospasm or apnoea (e.g. active pulmonary infection, patients younger than 3 months).
- Severe cardiovascular disease, such as angina, heart failure, or malignant hypertension (because of cardiovascular effects of ketamine, although this is controversial).
- CSF obstructive states (e.g. severe head injury, central congenital or mass lesions).
- Intracranial pressure pathology (e.g. glaucoma, acute globe injury).
- Previous psychotic illness (potential activation of psychoses)
- Hyperthyroidism or thyroid medication use (possibility of severe tachycardia or hypertension).
- Porphyria (possibility of triggering a porphyric reaction).
Preoperative Sedation / Analgesia (PSA)

Procedural Sedation and Analgesia

Definitions (SASA)

The definition of PSA encompasses a continuum of an altered state of consciousness, varying from minimal sedation/anxiolysis to deep sedation.

A  Non-dissociative sedation

Non-dissociative sedative drugs (including opioids, benzodiazepines, barbiturates, etomidate and propofol) operate on the sedation-dose response continuum. Higher doses provide progressively deeper levels of sedation with possible respiratory and cardiovascular compromise, a loss of protective reflexes and general anaesthesia. With the use of non-dissociative drugs, the key to minimising adverse events/complications is the careful titration of drugs to the desired effect.

B  Dissociative sedation

Dissociative sedation, produced with ketamine, causes a trancelike cataleptic state, characterized by intense analgesia, amnesia, sedation, retention of protective reflexes, spontaneous breathing and cardiovascular stability. When ketamine is administered in doses used for PSA, it does not operate on the sedation continuum and should not lead to loss of consciousness.

Sedation Spectrum Sedation

1. Anxiolysis: the patient is alert but calm
2. Light sedation: Easily roused patient and responding to Verbal commands
3. Deep sedation: patient is poorly rousable and responds to tactile stimuli
4. General anaesthesia: Unrousable patient
According to the mentioned sedation spectrum general anaesthesia should be avoided in PSA. This in fact is difficult to achieve for many reasons:
1. most of the drugs used in sedation are anaesthetics lacking analgesic properties and tend to produce respiratory and CVS depression
2. patient drug response variability


Compared with other anaesthetic agents, there is relative preservation of airway reflexes and tone. Ketamine stimulates saliva and tracheobronchial secretion, reduced by the use of an antisyialogogue (atropine or glycopyrrolate) to diminish this side effect, particularly in children.

The known effects of ketamine eg. Sympathetic stimulation, delirium, ataxia, nystagmus, myoclonus, random limb movements, and opisthotonus, are rarely clinically important with the doses recommended for PSA.

<table>
<thead>
<tr>
<th>Table 1: The continuum of sedation and sedation endpoints</th>
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<tbody>
<tr>
<td><img src="image" alt="Table Image" /></td>
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</tbody>
</table>

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Ketamine can be given via multiple routes (see Table)

**SASA Sedation Guidelines 2010**

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose</th>
<th>Onset</th>
<th>Time to peak effect</th>
<th>Duration of action(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>4 – 6 mg/kg as single agent 2 mg/kg if used with other sedatives/analgesics</td>
<td>&gt; 5 minutes</td>
<td>30 minutes(^a)</td>
<td>4 – 6 hours</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0.5 – 1 mg/kg(^a)</td>
<td>&lt; 1 minutes</td>
<td>3 – 5 minutes</td>
<td>5 - 10 minutes</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>2 – 4 mg/kg</td>
<td>2 – 5 minutes</td>
<td>20 minutes</td>
<td>30 minutes(^a)</td>
</tr>
<tr>
<td>Rectal</td>
<td>4 – 6 mg/kg</td>
<td>&gt; 5 minutes</td>
<td>30 minutes(^a)</td>
<td>30 – 120 minutes(^a)</td>
</tr>
<tr>
<td>Nasal</td>
<td>5 mg/kg</td>
<td>10 minutes</td>
<td>20 minutes</td>
<td>1 hour</td>
</tr>
</tbody>
</table>

Ketamine can be used in combination with other agents for PSA and for preoperative premedication

**Ketamine and Midazolame**

A low-dose combination of oral midazolam and ketamine as well as oral midazolam alone (0.25 mg/kg midazolam mixed with 1mg/kg ketamine in 5-ml honey and 0.5 mg/kg midazolam respectively), effectively reduce the stress during intravenous cannulation in children undergoing CT imaging without any adverse effects. However, the combination provides more children in a calm and quiet state when compared to midazolam alone at venipuncture.(6)

**Ketamine and Propofol (Ketofol)**

“Ketofol” is a combination of ketamine and propofol and is fast gaining popularity in the field of PSA. There is synergism between propofol and ketamine and combination therapy allows the use of lower doses of both drugs, thereby minimising side effects.
It can be prepared in a 1:1 ratio of 10 mg/ml ketamine and 10 mg/ml propofol in the same syringe. This equates to 5 mg/ml of ketamine and 5 mg/ml of propofol. A 70 kg patient can be given a bolus of 3 ml over 1 - 2 minutes. This should provide analgesia and sedation for 10 - 15 minutes. (8)

The addition of ketamine to propofol is thought to counteract the cardiorespiratory depression that occurs when propofol is used alone, whereas propofol blunts the psychomimetic and nauseant effects of ketamine. Ketamine provides an analgesic effect that is absent when propofol is used alone, which, for some clinicians, may represent a further advantage. Using ketamine and propofol in combination allows sedation to be achieved with lower total doses of each drug, resulting in favorable adverse event and recovery time profiles. Short recovery time is a valuable attribute of a procedural sedation and analgesia regimen in the Emergency department (ED) environment. (9)

Minar JR and et al (12) studied the occurrence of subclinical respiratory depression (change in ETCO2 of >10 mm Hg, and oxygen saturation of <92% at any time or addition of O2 and manipulation of the airways) and duration of recovery of ketamine vs propofol in procedural sedation and analgesia in ED. He concluded that, the use of either ketamine or propofol is safe and effective for procedural sedation in the ED.

Erden I et al compared the use of combined propofol 0.5mg/kg + ketamine 0.5mg (group1) with 0.5 mg/kg propofol+ketamine 0.25mg/kg(group2) in invasive diagnostic and therapeutic interventional radiological procedures.

There were no significant differences between the two groups with respect to demographic characteristics and the duration of the interventional radiological procedure, hemodynamic data, oxygen saturation, or side-effects. However, the mean propofol dosage was higher in group 2 than in group 1 and the number of over sedated patients (sedation score >4) was higher in group 2 than group 1, patients in group 2 required additional propofol during the procedure. The mean recovery times were 12.1±1 minutes in group 1 and 13.8±0.8 minutes in group 2 (P>0.05).

In conclusion, the two different dosages of ketamine coadministered with propofol for sedation during interventional radiological procedures showed no clinically significant hemodynamic changes or side effects. Both appeared to prompt early recovery time, so propofol 0.5 mg•kg-1 + ketamine 0.5 mg•kg-1 for sedation and analgesia during interventional radiological procedures, is recommended rather than propofol 0.5 mg•kg-1 + ketamine 0.25 mg•kg-1 because the former combination is associated with reduced rescue propofol requirements and therefore less oversedation.
Ketamine and Nitrous Oxide

Babl FE, et al. (7) has studied the safety of use of a ketamine nitrous oxide combination in paediatric procedural sedation in emergency department for 4 years recruiting 2002 patient. 89% of the patient showed no complication and the others had no serious adverse effect.

Guideline for Ketamine sedation of children in Emergency Departments

This guideline adopted by the clinical effectiveness committee of the college of emergency medicine UK

Summary of recommendations

1. Before ketamine is used all other options should be fully considered, including analgesia, reassurance, distraction, entonox, intranasal diamorphine, etc.
2. The doses advised for analgesic sedation are designed to leave the patient capable of protecting their airway. There is a significant risk of a failure of sedation if the procedure is prolonged, and the clinician must recognize that the option of general anaesthesia may be preferred in these circumstances.
3. There is no evidence that complications are reduced if the child is fasted, however traditional anaesthetic practice favours a period of fasting prior to any sedative procedure. The fasting state of the child should be considered in relation to the urgency of the procedure, but recent food intake should not be considered as an absolute contraindication to ketamine use.
4. Ketamine should be only used by clinicians experienced in its use and capable of managing any complications, particularly airway obstruction, apnoea and laryngospasm. The doctor managing the ketamine sedation and airway should be suitably trained and experienced in ketamine use, with a full range of advanced airway skills.
5. At least three staff are required: a doctor to manage the sedation and airway, a clinician to perform the procedure and an experienced nurse to monitor and support the patient, family and clinical staff. Observations should be regularly taken and recorded.
6. The child should be managed in high dependency or resuscitation area with immediate access to full resuscitation facilities. Monitoring should include ECG, blood pressure, respiration and pulse oximetry. Supplemental oxygen should be given.
7. After the procedure the child should recover in a quiet, observed and monitored area under the continuous observation of a trained member of staff. Recovery
should be complete between 60 and 120 minutes, depending on the dose and route used.

8. There should be a documentation and audit system in place within a system of clinical governance.

**Potential Complications of Ketamine sedation in children**

- Noisy breathing: usually due to airway mal-position and occurs at an incidence of <1%.
- Vomiting: 5-10% incidence. This usually occurs during the recovery phase.
- Lacrimation and salivation: 10% incidence
- Transient rash: 10% incidence
- Transient clonic movements: <5%

These complications and post operative patient care should be explained to the parents in details.

**Other use for Ketamine**

- Sedation (especially pediatric) away from the Operating Room
- Cardiac catheterization
- Radiation treatment
- Radiologic studies
- Dressing changes (e.g. post burn injury)
- Dental procedures

**KETAMINE IN CHRONIC PAIN MANAGEMENT**

**Physiology of pain**

**Primary afferent fibers and the dorsal horn**

Peripheral nociceptives are organs that respond to pressure, temperature, and chemical stimuli. The nociceptive cells are located in dorsal root ganglia except head and neck where they are located in trigeminal ganglia.

2 main types of nociceptors

1. High threshold fibers include A fibers and C fibers stimulated by inflammatory soup
2. Silent nociceptives become active in case of inflammation and play a role in peripheral sensitization.
• The dorsal horn is made out of lamina I-X
• Lamina I consists of mainly A fibers
• Lamina II is called substantia gelatinosa and contain mainly C fibers and no ascending tracts originate from this area
• Lamina III—IV contain interneuron
• Lamina V contain the WDR neuron (high threshold)
• Lamina IX represent only motor neuron and Lamina X is made of visceral neuron

Primary afferent fibers interact extensively with other afferents as well as second order neurons and endings of descending fibers. 2nd order neurons are divided into high threshold neurons (nociceptive specific) and “wide dynamic range “ neurons. When sensitized, the WDR neurons respond to non noxious stimuli (allodynia)

Role of NMDA Receptor in Chronic pain

Release of glutamate and substance p from the nociceptive primary afferent activates the low threshold AMPA and NK1 receptor, which in turn activates the NMDA receptor. Removal of Mg plug is followed by influx of Ca into the cell and production of NO and secondary messenger. In addition, C fos gen expression occurs within minutes of painful stimulus and works as a marker for noxious stimulation. C fos is thought to be the link between acute and chronic pain.

Central sensitization results from activation of N-methyl-D-aspartic acid (NMDA) receptors leading to hyperalgesia “wind up “ and LTP (long term potentiation ) that represents increased activity in dorsal horn followed repetitive stimulation. Repetitive low threshold stimulation results in phenomena of “wind up “ and temporal summation. The phenomena represent an increase in the intensity and a decrease in the threshold in the spinal cord.
Ketamine is an NMDA antagonist with the potential to provide analgesia and modulate development of chronic pain.

Ketamine also potentiates the descending inhibitory pathway which modulates the nociception at the level of dorsal horn. Ketamine enhances the inhibitory neurotransmitters involved in this pathway such as noradrenalin, 5HT and GABA.

**Progression of acute pain to chronic pain**

With the onset of chronic pain including CRPS((complex regional pain syndrome)) a number of changes in brain function occur in the human brain, including but not limited to: (1) central sensitization (2) functional plasticity in chronic pain and in CRPS, (3) gray matter volume loss in CRPS (4) chemical alterations and (5) altered modulatory controls. Such changes are thought to be in part a result of excitatory amino acid release in chronic pain. Excitatory amino acids are present throughout the brain and are normally involved in neural transmission but may contribute to altered function with excessive release producing increased influx of calcium and potentially neural death.

Ketamine may by mechanisms that include reducing phosphorylation of glutamate receptors, results in decreased glutamatergic synaptic transmission and reduced potential excitotoxicity.
Oral Ketamine in treatment of Chronic Pain

Oral formulations of ketamine are not commercially available. The parenteral formulation is given as an oral solution or an extemporaneous preparation is made. M I Block and et al(11) have reviewed articles from 1966 -2009 regarding efficacy and safety of use of oral ketamine in the management of chronic pain. From 88 articles, they only included 22 in the study and the others were excluded.

Two approaches to pain treatment with oral ketamine were described. Either the patient started directly with oral ketamine with a low daily dose which based on clinical effect and/or adverse effects, is increased. Or, the patient started with parenteral ketamine, either a single test dose or continuous treatment with usually intravenous or subcutaneous ketamine, after which the patient is switched to an equipotent oral dose of ketamine. The effective daily dosages ranged from (approximately) 45 mg to 1000 mg. Equianalgesic potency of ketamine subcutaneous/ketamine per os in daily dose ranged from 1:0.3 to 1:8.5, with a median of 1:1.

It was concluded, that efficacy and long-term adverse effects are insufficiently studied to promote the routine use of oral ketamine in chronic pain management. Some of the studies on oral ketamine show a disappointing success rate, either due to treatment failure or appearance of adverse effects. Wide clinical use of ketamine is limited due to psychomimetic and other adverse effects. On the other hand, ketamine as an analgesic has proven to be of effective in patients with severe pain who have failed to respond to routine pharmacotherapy. In these patients with intractable pain the use of oral ketamine can be beneficial. From that perspective, oral ketamine may have a limited place as add-on therapy in complex chronic pain patients.

Yaser Amr,(19) conducted a study of multi day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. This double-blind study sought to determine the safety and efficacy of adding a multi-day low dose ketamine infusion to oral gabapentin for the treatment of chronic pain related to post spinal cord injury. He concluded that ketamine addition to gabapantine in post-spinal cord injury related chronic pain is safe and efficacious in reducing pain, but the effect compared to placebo ceased 2 weeks after infusion termination. The study size limited to 40 patients.
Ketamine as an adjuvant to Neuraxial Block

Addition of ketamine 0.5 mg.kg(-1) and clonidine(1 microg.kg-1) to ropivacaine 0.2% 0.75 ml.kg(-1), when Ketamine prolongs the effect of local anaesthetic (e.g. ropivacaine) and decreases the postoperative analgesic requirement when given caudally in children undergoing inguinal hernia repair (Odeş R et al)(22). Ketamine in South Africa is unsuitable for neuraxial use due to the presence of neurotoxic preservatives. When administered caudally in children, prolongs the duration of postoperative analgesia. The need for subsequent postoperative analgesic is also reduced. Caudal analgesia attenuates or allows partial changes to postoperative cortisol, insulin or blood glucose responses to surgery. Akbas M.et al (23)

Prehospital use of Ketamine

Use of ketamine in prolonged entrapment (21)

An ideal analgesic agent for use in entrapments should provide rapid, effective pain relief with no vomiting or respiratory depression. The airway and gag reflex should be maintained. Neurological or cardiovascular adverse effects should be insignificant, even in the hypovolaemic patient. It should also be environmentally robust.

Entonox can be given by suitably trained ambulance staff, but it involves relatively bulky equipment, separates into its component gases on cooling (which can occur after as little as 15 min of use in low ambient temperatures), and cannot be used if the patient is uncooperative or has facial or chest injuries. Side effects of commonly used opiates, such as pethidine or morphine, include hypotension (particularly in the presence of hypovolaemia) and vomiting. Respiratory depression and loss of the airway may lead to life-threatening hypoventilation if access to the face and neck is limited.skillful paramedics may be able to use nalbuphine, although this opioid has also been associated with nausea and vomiting, even if respiratory depression is not marked. It also has a ceiling of pain relief equivalent to approximately 10 mg of morphine.

Ketamine can be given intravenously, intramuscularly, intrathecally, and even orally and rectally. It provides analgesia in low dose (0.4mgkg) that slides imperceptibly into dissociative general anaesthesia at higher doses (2-4mgkg-1 by intravenous injection) without losing the airway. Marked bronchodilatation has been an unexpected benefit. Loss of the airway is reported as being extremely rare. Ketamine tends to maintain the blood pressure, even in the presence of hypovolaemia.
Ketamine in Labour Pain (25)

In sub-anaesthetic doses, ketamine has been used in late labour or at delivery, as given in the next table. Psychomimetic effects have been a major disadvantage, though in labour, delirium and unpleasant dreaming is infrequent.

![Table 3: Low dose ketamine analgesia](image)

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<table>
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<tbody>
<tr>
<td>1.</td>
<td>Antacid prophylaxis</td>
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<td>2.</td>
<td>Pre-anaesthetic evaluation</td>
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<tr>
<td>3.</td>
<td>I stage labour: Bolus 10-15 mg then infusion 0.5-1 mg kg⁻¹ min⁻¹</td>
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<tr>
<td>4.</td>
<td>Monitor sensorium</td>
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<tr>
<td>5.</td>
<td>At crowning, 0.2-0.4 mg kg⁻¹ (total dose 12.5 mg-25 mg) don't exceed 100 mg</td>
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Ketamine and Opioid Tolerance (24)

Opioid analgesia is used commonly in the treatment of acute and chronic pain. In a small but significant number of patients (less than 5%), it may provide insufficient analgesia, especially if used as a sole analgesic. Tolerance may be due to;

- Alteration in G protein coupling to opioid receptor
- Changes in receptor trafficking between the neural surface and cytoplasm
- Central sensitization and increased NMDA receptor sensitivity.

Types of opioid tolerance

Early -->30mg Morphine / 4hrs
Delayed -->80 mg Morphine / 24 hrs

Management of Opioid Tolerance (24)

Multimodal approach

1. Anti hyperalgesic drugs
   Because acute or chronic pain are deemed to be nociceptive/inflammatory in nature, patient will benefit from the paracetamole and NSAID unless there are contraindications.
2. Add appropriate adjuvant
Patients who have no previous chronic pain are usually treated with opioids alone or with NSAID but usually there is some neuropathic element in patients of chronic pain so adjuvant agents are needed such as:
- Tricyclic antidepressants- eg amitryptyline 10-75 mg at night
- Anticonvulsants; eg gabapentin 100-200mg BD-TDS, pregabalin 25-300mg daily or clonazepam 0.5-3mg BD

3. Addition of regional block especially with use of catheter technique and continuous wound infiltration. A few patients can benefit from implantation of a continuous epidural or spinal catheter that can be refilled as outpatient.

4. Additional opioid medications

5. Opioid “re-sensitisers”
- Opioid rotation there are significant differences in the interaction between different mu agonists. Accordingly, a patient who is experiencing inadequate analgesia from one opioid, may get good effect from another one, eg switch to slow release morphin or transdermal fentanyl and after a while switch back to previous drug when tolerance to the last one is developed.
- Ketamine NMDA receptors are central in the pathogenesis of chronic pain and in opioid tolerance due to up regulation of NMDA receptors. Administration of low doses of ketamine has been shown to restore opioid sensitivity for prolonged periods.
- As follow peroperative dose: 0.5 mg/kg on induction, repeated 30 minutes prior to estimated emergence for operation lasting longer than 2 hours.
- PCA: ketamine may be mixed with an appropriate opioid at concentration of 1-3 mg/ml eg ketamine 100mg + morphin 100mg in 50ml saline given 1ml bolus with 10 minutes lockout. Or fentanyl 2.5mg + ketamine 250 mg in 50 ml saline given as a 1ml bolus and 10 minutes lockout.
- Oral ketamine: has extensive first pass metabolism therefore a dose of 5mg/kg is required. A typical mixture is morphine 5mg/ml with ketamine 10 mg /ml given as a dose of 5ml 1-4 hourly as needed.
- Leo Kapural, et al (15) Outpatient intravenous ketamine infusions did not improve long-term pain scores in patients with high opioid requirements and only a few were able to substantially reduce opioid use. Considering infusion risks and cost of such outpatient treatment, ketamine infusions do not appear to be a feasible option for improving pain relief and decreasing opioid use in high-opioid requirement patients.

In conclusion, repeated ambulatory intravenous ketamine infusions did not consistently produce long term (more than 6months) reductions in pain or opioid use in patients with severe chronic pain. But patients with opioid tolerance may benefit from the ketamine re-sensitizing effect on opioid receptors. However, this study was not randomized.
6. Alpha-2 agonist
   - Dexmedetomidine 200mcg + ketamine 250mcg + fentanyl 2.5mg + granisetron 3mg dosed with 1mg bolus and 10 minutes lockout.
   - Dexmedetomodine 200mcg + ketamine 250mcg + morphine 500 mg + granisetron 3mg dosed with 1mg bolus and 10 minutes lockout.

**Ketamine in Head Injury**

Ketamine causes increased catecholamine release and decreased norepinephrine (noradrenaline) re-uptake which results in increased heart rate, arterial pressure, and MAP. This makes it a useful analgesic for trauma patients who may already be haemodynamically compromised. A single episode of hypotension is associated with a worse outcome. Head injury increases concentrations of glutamate, which induces neuronal apoptosis. Ketamine blocks the actions of glutamate on the NMDA receptor, which may protect against cellular neurotoxicity, but this has yet to be demonstrated in human studies.

Despite these benefits, the use of ketamine in patients with head injuries remains controversial. Early studies suggested that the use of ketamine may have resulted in
a transient increase in ICP in a small number of patients. CPP was compromised only in the patients with pre-existing intracranial hypertension and obstruction to the flow of cerebral spinal fluid. This has; however, led to the persistent belief that ketamine is contraindicated in patients with traumatic head injuries.(19) Studies done subsequently have shown, however, that the effects of ketamine on cerebral haemodynamics and ICP are in fact variable and depend on both the presence of additional anaesthetic agents and PaCO2 values.

When ketamine is used in the presence of controlled ventilation, in conjunction with anaesthetics which reduce cerebral metabolism such as c-aminobutyric acid (GABA) receptor agonists, ICP is not increased. Management of the severely head injured patient should focus on minimising secondary brain injury. Ketamine is a cardiorespiratory stable analgesic, which when used in combination with midazolam provides good sedation and has not been shown to increase ICP adversely. This, combined with the potential neuroprotective effects of NMDA antagonism, could improve neurological outcomes in brain injury.(20)
Conclusions: Ketamine for Traumatic Brain Injury

- Ketamine is the most widely used anesthetic in the world (Ducharme J Emerg Med 2001:13;7-8)

- Early studies performed showing increased ICP were in patients with non-traumatic intracranial lesions, often with CSF flow obstruction. They do not apply to TBI because compensatory mechanisms of CSF, venous blood and brain tissue distribution are intact (Langfitt TW Clin Neurosurg 1968;16:436-471). Therefore increased CBV can occur without causing a large increase in ICP. A rise in ICP with ketamine is accompanied by a rise in systemic BP, CPP and CBF.

- Vasoresponsivity to CO2 is retained with ketamine. In the setting of multiple trauma with hypotension and traumatic brain injury, ketamine can maintain CPP. In experimental model of hypovolemia and increased ICP, ketamine increased CPP with a small change in ICP (Klose R et al Anaesthesist 1982:31:33-38). The current practice of avoiding ketamine in rapid sequence intubation for traumatic brain injury is not evidence based.

Ketamine as Antidepressant  (26)

Scientists aren’t quite sure why modern antidepressant drugs succeed or fail to cure depression in different patients. Most of today's drugs target a particular class of neurotransmitter called the biogenic amines. These include serotonin, which is targeted by selective serotonin reuptake inhibitors, or SSRIs. Fluoxetine and sertraline, are members of this enormously popular category of drugs. But these kind of drugs take weeks to work, and fail to help at least 40% of depressed patients. So neuroscientists suspect that these drugs don’t hit depression at its source and are searching for other approaches.

The search took a dramatic turn in 2006 when a team led by Husseini Manji, at the National Institute of Mental Health in Bethesda, Maryland, published a study looking at the effects of ketamine on 18 severely depressed patients, all of whom had failed to respond to standard treatments. In the double-blind trial, doctors gave the patients intravenous ketamine or placebo saline drips, and then scored the responses. After taking ketamine, 12 of the patients improved by at least 50% on a depression rating scale. Patients felt better as little as two hours after treatment. And one-third of the patients still felt better a week later. Same finding was proved by other study led by Krystal at Yale.
One possible explanation for this is that ketamine uses different pathways to trigger its psychedelic and antidepressant effects. Another possibility is that patients have to go out of their minds before they can get back to normal. “What ketamine does is briefly make people crazy,” says Eric Nestler, neuroscientist and psychiatrist. It is already known that stress floods the brain with glutamate, says Zarate. “It might be that these neurons are struggling to regulate glutamate, and if you stress them over and over, they become injured.

This hypothesis is still very new. There is some evidence linking glutamate, and the NMDA receptor, to depression. Twenty-five years ago, for instance, scientists at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland, showed that chemicals that target the NMDA receptor have antidepressant effects in animals.

Scientists have since found that deceased depressed human patients, such as suicide victims, have abnormal numbers of NMDA receptors. And brain-imaging studies have found that depressed people have much higher levels of glutamate in one region of their brains than that in healthy people. But some psychiatrists caution that it is impossible to know yet whether ketamine affects brain-cell survival. Glutamate is the most common neurotransmitter in the brain, used by perhaps half of all brain cells and the NMDA receptor is involved in a huge array of different processes, such as learning and memory, as well as cell growth and survival. So it is difficult to pin down the precise reason why tweaking glutamate through the NMDA receptor would influence human happiness. And although it is true that the NMDA receptor is involved in cell survival, this takes a long time, whereas ketamine’s antidepressant effects seem to kick in within hours.
CONCLUSION

It can be concluded that ketamine is under estimated. The known side effects of ketamine are dose related and can be easily attenuated. In addition, ketamine is proved to be safe drug for induction and analgesia and recommended to be the first drug in the peripheral and field hospital. Also the only drug recommended for use by the paramedics in the prehospital setting.

The traditional contraindication of use of ketamine in head injury is conflicting and inconclusive. Ketamine needs more concern by the practioners because theoretically it is an Ideal Induction drug because:

- Can be given orally, IM, or IV
- Provides Anesthesia, Amnesia, Analgesia
- Rapid onset
- Maintains cerebral blood flow
- Maintains protective airway reflexes
- Maintains hemodynamic stability
- Reverses bronchospasm
- Anti-inflammatory
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