



BMH Med. J. 2017;4(3):84-90 **Review Article**

## Versatility of Ketamine

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### Abstract

In the present day anaesthesia practice, ketamine is not routinely used as an induction agent. But it is a popular pharmacological agent in variety of pain conditions from nociceptive to neuropathic pains and for paediatric procedural sedation outside operation theatre complex. Of late, there is a renewed enthusiasm with regard to use of Ketamine for variety of indications like pain relief in pre hospital trauma victims, as an antidepressant, anticonvulsant, to prevent post operative sore throat and even in renal colic.

Following text is a narrative review on the recent evidences with regard to pharmacology of the agent for its extended indications other than in day to day anaesthesia practice.

**Keywords:** Ketamine, Neuropathic pain, Trauma pain, Burns dressings

### Introduction

Since its introduction into clinical practice, prescription of ketamine for more than half a century was entirely in the domain of anaesthesiologists. It binds to the phencyclidine receptor of the N-methyl D-aspartate (NMDA) channel noncompetitively and inhibits activation of receptors by glutamate. Ketamine was once a popular agent for induction of anaesthesia in patients with relative hypovolaemia or for short surgical procedures. In most of the so called emerging pharmacological indications of ketamine, it is used in subanaesthetic doses. The perceived advantage at this therapeutic range is that it causes little or no respiratory depression but at the same time maintaining airway tone and reflexes unlike other induction agents. When used in sub anaesthetic doses there is no or mild psychotomimetic effects with good patient acceptance. But it must be recognized that ketamine is an anaesthetic agent and the user should have the competence and confidence in handling airway compromise if need arises.

The commercial preparation of ketamine which is commonly available consists of two enantiomers in equimolar amounts [1]. Out of this, the S(+) ketamine has four fold greater affinities to N methyl D aspartate receptors (NMDA) than R(-) ketamine, but with shorter duration of action [1]. The S(+) ketamine is now available as a preparation for clinical use.

### **Procedural sedation**

Routine use of ketamine as an induction agent is limited due to unpleasant psychomimetic effects. But because of its ability to maintain airway reflexes even while providing adequate levels of sedation makes it an attractive option for procedural sedation, especially in paediatric practice. Its relative safety makes it a practical option in situations which lack sophisticated equipments and monitors as in military practice, emergency department and in procedural sedation outside the operation theatre. Ketamine is used alone or in combination of other agents like Propofol for this purpose.

In our present day practice, use of ketamine is common in cardiac catheterization, gastrointestinal endoscopy, paediatric radiological investigations and radiotherapy. Though it can be administered by different routes, intravenous one is considered superior [2] because of more predictable effects. Most anaesthesiologists prefer to have an IV access in situ as a precautionary measure and with the advantage of giving top up doses, if the need arises.

### **Trauma victims**

Ketamine produces predictable and profound analgesia with both intramuscular and intravenous administrations. It is an attractive option as an analgesic in trauma patients [3]. Especially in subanaesthetic dosage it is a safe alternative to opioids in prehospital care of polytrauma victims [4]. It avoids the potential drop in blood pressure and respiratory depression that is sometimes associated with the use of opioids. Airway related problems are also less compared to opioids, but there is risk of hallucinations and agitations with ketamine compared to opioids [5].

In low resource rural trauma situations, ketamine proved to be safer alternative to opioids as was evident from a ten year cohort study from Iraq [6]. Jennings PA et al in a out of hospital, randomized, controlled study established the superiority of intravenous morphine plus ketamine combination over intravenous morphine alone in out of hospital adult trauma patients. But the combination is also associated with some increase in the rate of minor adverse effects [7]. A recent meta analysis of six trials indicates the favourable effects of ketamine over opioids, establishing itself as a key agent for pain control in trauma patients [8].

### **Post operative pain**

It was Sadove et al who first suggested the use of ketamine as an analgesic in sub anaesthetic doses [9]. Since then there is growing literature evidence to support the efficacy of ketamine in variety of pain conditions. Parikh B et al in sixty American Society of Anaesthesiologists (ASA) I and II patients for elective renal surgeries found that small dose of ketamine before skin incision (0.15mg/kg) and continued as infusion (2microgram/kg/minute) during procedure is effective in reducing post operative morphine requirements [10]. The analgesic potency of ketamine at this subanaesthetic dose is explained by the inhibiting action on the NMDA receptor mediated pain facilitation [11]. Bell RF et al in a meta analysis involving 37 trials found ketamine to be effective in reducing morphine requirements in the first 24 hours after surgery [12]. Incidentally there is also reduction in post operative nausea and vomiting with fewer adverse effects reported [12]. Ketamine was also found to be a useful adjuvant when used along with local anaesthetics in both central neuraxial blocks and peripheral plexus blocks [13]. However only preservative free ketamine should be used in central neuraxial blocks. Marc De Kock described perioperative use of intravenous ketamine (0.5mg/kg bolus) followed by 0.25mg/kg/hr to reduce wound hyperalgesia and can be used as a useful adjuvant in balanced analgesia [14].

### **Neuropathic chronic pain**

The rationale in prescribing ketamine for neuropathic pain is the concept that hypersensitivity of

NMDA receptors is responsible for the genesis of neuropathic pain and ketamine is a potent NMDA receptor antagonist [15]. At subanaesthetic dose, the analgesic efficacy parallels with its inhibitory action on the NMDA receptor mediated pain facilitation. Ketamine was tried through different routes (intravenous, subcutaneous, oral, topical, intranasal) and proved to be efficient in different neuropathic pain conditions [15]. Bioavailability with oral and sublingual preparations is around 25%. There is even a gel based oral preparation for topical application [16].

There are case reports wherein ketamine infusion is associated with significant pain relief in complex regional pain syndrome type-1 (CRPS-1) [17] and is investigated as a modality of treatment [18]. It has proved its worth not only in CRPS-1, but also in other chronic neuropathic conditions such as central pain, fibromyalgia and in post ischaemic pain [19]. A recent randomized controlled trial showed that a ketamine regimen is superior to methadone or ketamine combined with methadone in alleviating neuropathic pain [20]. Another indication for ketamine is in pain relief for chronic opioids-tolerant patient when all other options have exhausted [21]. Allodynia, resulting from nerve injury responds poorly to opioids and ketamine has been reported to reduce this discomforting problem [22]. Ketamine though can't be prescribed on long term basis, is found to be useful as a short term therapy in central post-stroke pain [23].

### **Burns dressings**

Ketamine is used extensively in burns ICUs and in operation theatres for burns dressings and for minor tangential excisions and skin grafting. It is especially useful in paediatric patients who are anxious about the repeated procedure and pain. With sub-anaesthetic ketamine, both primary and secondary hyperalgesia is also found to be less. To minimise emergence phenomenon, pre-treatment with benzodiazepine is ideal. A prospective study conducted by Mac Pherson RD, et al concluded that a patient controlled analgesia technique by a combination of ketamine/midazolam provided adequate and effective analgesia for burns dressings [24]. Recovery time after a continuous administration may be prolonged. Patients who require repeated administration may develop tolerance, i.e., they require increasing subsequent doses. In a randomized double blind cross over study, Pankaj Kundra et al clearly showed the superiority of oral ketamine as an analgesic compared to dexmedetomidine in adult burn dressings [25.] But the use of ketamine was associated with delirium and excessive salivation [25].

### **Phantom limb pain**

Hyperactivity of NMDA receptors is believed to be one of the mechanisms for the maintenance of phantom limb pain (PLP). Hence ketamine may have a role in the treatment of PLP. Successful use of oral ketamine to reduce the intensity of phantom limb pain has come in literature [26, 27].

### **Anticonvulsant!**

An interesting case report appeared in Annals of Pharmacology by Diane et al in 2013 where ketamine infusion was used to control refractory status epilepticus in a patient with anticonvulsant hypersensitivity syndrome [28]. There are animal studies and literature evidence to say that ketamine indeed has antiepileptic properties. But it is difficult to conclude and analyse from the many reported cases as patients were on multiple antiepileptic medications [29].

### **Antidepressant!**

Present therapeutic options for major depressive disorder takes weeks to achieve the desired effects. On the other hand, patients given ketamine found to have antidepressant effects within few hours. This made researchers to think of new generation fast acting antidepressants by modulating NMDA

receptors. Interestingly when other NMDA receptor antagonists were tested clinically, they have only modest antidepressant effects compared to ketamine but with less dissociative effects [30]. Zhang JC et al in animal studies demonstrated R(-) ketamine to have greater potency and long lasting antidepressant effect than the S(+) enantiomer [31]. Interestingly ketamine also was shown to rapidly reduce suicidal thinking [32]!

### **Renal colic pain**

Renal colic pain is usually very intense and require very strong analgesics. In a recently published randomized double blind controlled trial performed in 53 patients with renal colic, Farnia MR et al demonstrated the effectiveness of intranasal ketamine in relieving renal colic pain [33]. However ketamine is not yet a popular agent as the first line therapy for renal colic pain and there is paucity of studies on the topic.

### **Prevention of Post operative sore throat**

Post-operative sore throat is a vexing problem for anaesthesiologists. Different pharmacological agents are being tried to prevent occurrence of sore throat in the post-operative period. O Canbay et al in a randomized, placebo-controlled, single blind study observed that preoperative ketamine gargling significantly lowered the incidence and severity of post-operative sore throat [34]. However such beneficial effect is not observed with intravenous ketamine [35].

### **Neuroprotective action**

Neuroprotective role of ketamine contradicts the conventional teaching of anaesthesiologist, wherein it is relatively contraindicated as it increases intracranial pressure. Recent enthusiasm to apply the drug as a neuroprotective agent stems from two basic understandings: (1) Mechanism of action of ketamine i.e. non-competitive antagonism at NMDA receptors, (2) Increase in intracranial pressure it produces may not be relevant in the presence of normocapnia and stable blood pressure. In animal experiments, ketamine has been shown to attenuate the damage in the caudoputamen of hypocapnic rats [36]. But at present, evidence is inconclusive to recommend the use of ketamine as a neuroprotective agent.

### **Summary**

Ketamine was introduced into clinical practice in 1960s. But with the advent of new pharmacological agents and because of undesired psychic actions, ketamine is slowly taken off from the drug cart of anaesthesiologist in the operation theatre. Outside operation theatre its role as an analgesic for the pre hospital trauma victims as well as in emergency minor procedures in casualty environment, chronic neuropathic pain, burns dressings and for paediatric procedure sedation are all established. But what is interesting is clinical and experimental evidence of its role in new frontiers like anticonvulsants, antidepressants, neural protection and even to blunt post operative sore throat. For the time being ketamine is not the first choice drug in these scenarios. We need more data to clearly recommend its use for these emerging indications.

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