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# Ketamine for Non-Neuropathic Pain

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## Abstract

Chronic pain is one of the leading causes of years lost to disability, as most of the time it is refractory to conventional treatment. Recent advances in understanding the pain mechanisms have favored the use of ketamine as a rescue agent in refractory chronic pain conditions, as it has potential modulating effect on both sensory-discriminative and affective motivational components of pain. Preclinical studies also suggested the antinociceptive effect of sub anesthetic dose of ketamine against central and peripheral neuropathic pain conditions and non-neuropathic pain conditions such as inflammatory and nociceptive pain states. Subanesthetic infusion of ketamine along with adjuvants such as midazolam and clonidine is found to reduce the psychomimetic and cardiovascular side effects of ketamine. Even though the consensus guidelines for intravenous use of ketamine for chronic pain advocate the use of ketamine only for complex regional pain syndrome, various other clinical studies suggested its role in other refractory painful conditions. Hence the present topic focuses specifically on the effect of ketamine on non-neuropathic pain conditions such as complex regional pain syndrome, fibromyalgia, headache, ischemic limb pain, etc. Many studies had shown that ketamine not only reduces the pain scores but also the analgesic medications, which further improves the well-being and quality of life.

**Keywords:** ketamine, non-neuropathic pain, nociplastic pain, refractory pain syndromes, NMDA receptor antagonist

## 1. Introduction

Chronic pain (CP) is one of the most leading causes of disabilities affecting more than 30% of people worldwide [1–3]. It is a disease in its own right [4]. Individuals with moderate to severe pain experience a marked decrease in the physical, psychological, and social well-being. It further affects the quality of life, reduces the ability to perform routine activities, and leads to work absenteeism. Economic costs associated with the management of chronic pain in United States include direct healthcare costs ranging from \$260 to \$330 billion and indirect cost ranging from \$300 to \$350 billion per annum [5]. The leading causes of year lost to disability worldwide in 2013 include low back pain, neck pain, migraine, and musculoskeletal disorders [6].

Management of CP is often based on trial-and-error approach with tricyclic antidepressants, anticonvulsants, and narcotics. Many studies have also suggested that combination of drugs is superior to single agent for CP management [7]. Recent

advances in understanding the pain mechanism have favored the use of ketamine as a rescue agent in refractory chronic pain syndromes [8]. The most recent definition of neuropathic pain by International Association for the Study of Pain (IASP) excludes the pain states characterized by central sensitization in the absence of a discrete nerve injury such as CRPS-1 and fibromyalgia [8]. Further the new pain descriptor nociplastic pain includes the condition associated with altered processing of pain that does not fit into nociceptive category such as fibromyalgia, CRPS-1, nonspecific chronic back pain, irritable bowel syndrome, and other functional visceral pain disorders [9]. Drugs used to be effective for one type of pain have been shown in various studies to be effective for other type of pain also [10, 11]. Even though the preclinical studies supported the antinociceptive effect of ketamine against central and peripheral neuropathic pain states, there is growing evidence suggesting its analgesic effect in inflammatory and non-neuropathic pain conditions also [12–14]. Hence the present topic focuses specifically on the effect of ketamine on non-neuropathic pain conditions.

## **2. Newer concepts of pain**

Pain can be classified as nociceptive, neuropathic, and nociplastic in origin. Nociceptive pain results from stimulation of primary nociceptive nerve endings by actual or threatened tissue damage, while integrity of nerve fibers is preserved. In contrast to nociceptive pain, neuropathic pain results from direct injury or disease affecting somatosensory nervous system. Recently defined nociplastic pain is the pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory nervous system causing pain. Characterization of altered nociception is yet to be defined [15]. Another widely used terminology is mixed pain. It is a complex overlap of various known pain types (nociceptive, neuropathic, and nociplastic) in any combination acting simultaneously and/or concurrently to cause pain in the same area [16].

### **2.1 Chronic pain**

Acute pain is reduced with the removal of painful stimulus, while chronic pain persists beyond the useful limit of pain signal and often extends beyond 3–6 months after the initial tissue injury has healed. IASP along with World Health Organization (WHO) proposed a new chronic pain classification for the 11th edition of International Classification of Diseases (ICD) as chronic primary pain and chronic secondary pain. Chronic primary pain is defined as the pain in one or more anatomical region that persists or recurs for longer than 3 months; it is associated with significant emotional stress and functional disability, and the symptoms are not better accounted for by another diagnosis. Chronic secondary pain is considered as a symptom of another condition, whereas in chronic primary pain, the pain itself is considered as a disease. These conditions often exhibit central sensitization along with psychological distress and pain catastrophizing. For example, chronic widespread pain, fibromyalgia (CRPS 1) temporomandibular disorder, irritable bowel syndrome, most back pain, and neck pain syndromes [17].

Approximately 30% of world's population suffer from chronic pain, and it is more common in females and in old population [18, 19]. Other risk factors include low socioeconomic status, geographical and cultural factors, and psychological factors such as anxiety and depression. Increase in prevalence may negatively affect the global health status and overall economy of countries [20].

Even though the acute pain or traumatic injury may proceed the development of chronic pain, mechanism behind the chronic pain may differ from those implicated in acute pain [21]. In contrast to acute pain, the diagnosis of chronic pain is not often straightforward. It often involves biomedical and psychological factors. Standardized questionnaires such as LANSS, Pain DETECT, and DN<sub>4</sub> are used to evaluate pain along with functional abilities and emotional distress in chronic pain patients. Detailed history, clinical examination and confirmatory tests are often necessary for presumption of diagnosis. Several studies have reported the successful short-term management of chronic nonmalignant pain with ketamine infusion.

### **3. Ketamine**

#### **3.1 History**

Ketamine initially labeled as CI-581 is a phencyclidine derivative prepared by Professor Calvin from Parke Davis. After experimental studies on animals, first human trial was conducted on prisoners on August 3, 1964 by Dr. Domino and Dr. Corssen. They found that ketamine could rapidly produce analgesia with unique state of altered consciousness, which was later named as “dissociative anesthesia” by Toni, wife of Dr. Domino. Because of its sympathomimetic effects and wide safety margin, ketamine was used as war anesthetic to American soldiers in Vietnam war [22].

#### **3.2 Ketamine and its isomers**

Ketamine [2-(2-chlorophenyl)-2-(methyalmino)-cyclohexanone ketamine] is a racemic mixture of two optical enantiomers [23]. S(+) ketamine is two times stronger than parent compound and four times stronger than R(–) ketamine. It has also anti-hyperalgesic effects [24]. R(–) ketamine has potent antidepressant effect [25]. Ketamine undergoes demethylation and hydroxylation and metabolites are conjugated and excreted in urine [26]. Nor ketamine is the main metabolite, and it is one-third to one-fifth as potent as its parent compound [27].

Ketamine can be safely administered through several routes with varying bio-availability: intravenous (100%), intramuscular (93%), oral (20%), nasal (50%), and rectal (20%) and even epidural [28]. FDA has approved the use of intranasal S (+) ketamine along with antidepressant in treatment-resistant depression [29].

#### **3.3 N-Methyl-D-aspartate receptor**

Discovery of N-methyl-D-aspartate (NMDA) receptor and its noncompetitive inhibition by ketamine has revolutionized the use of ketamine as a potent anti-hyperalgesic drug in various painful states.

NMDA receptors are important for learning, memory, and synaptic plasticity, and it is also involved in amplification of pain signals and opioid intolerance. Non-competitive antagonism of NMDA receptor by ketamine occurs by two different mechanisms. It decreases the frequency of channel opening by allosteric mechanism and reduces the time spent in the acute open state [30]. Ketamine equally binds to NMDA subtypes 2A to 2D and results in favorable effect compared with other subtype selective NMDA antagonists [31]. It inhibits NMDA-mediated responses both in spinal cord and thalamus. Its non-competitive antagonism allows the endogenous agonist glutamate to continue to binding to these sites. Ketamine at lower concentration blocks closed channels, while higher

concentration blocks both open and closed channels [32]. Ketamine can also interact with NMDA receptors present at periphery [33].

### **3.4 Action on other receptors**

Ketamine also binds to  $\mu$ ,  $\kappa$ , and  $\delta$  receptors; however, this interaction is not responsible for its analgesic effect as their block is not antagonized by naloxone [34–36]. At high doses it also produces local anesthetic effect by blockade of sodium channel receptors [37].

Ketamine's interaction with monoaminergic system is significant with the stimulation of non-adrenergic neurons and inhibition of catecholamine uptake, and it provokes hyperadrenergic condition (norepinephrine, dopamine, serotonin) [38]. R(–) isomer inhibits only neuronal uptake while S(+) isomer inhibits extra neuronal uptake also [22]. Ketamine also has a direct inhibitory effect on nicotinic and muscarinic receptors [39].

Ketamine also acts on other non-NMDA pathways that play significant role in pain and mood regulation including the blockade of Na-K channel (hyperpolarization-activated cyclic nucleotide gated (HCN), activation of high affinity D<sub>2</sub> receptors and L-type voltage-gated calcium channels, facilitation of gamma aminobutyric acid A (GABA-A) signaling, and enhancement of descending inhibitory pathways [32, 40, 41].

Ketamine can also block large conductance K<sub>Ca</sub> channels (BK channel) and preferentially suppresses spinal microglia hyperactivation after nerve injury, which may explain its potent effect against neuropathic pain [42]. Direct inhibition of nitric oxide synthase could also contribute to its analgesic and anesthetic properties [43].

## **4. Consensus guidelines of ketamine infusion for chronic pain**

Over the past few years, the use of ketamine infusion for the management of CP had increased dramatically but with wide variation in dose, monitoring, and selection of patients. This has led to the creation of consensus Guidelines to start ketamine infusion for CP by American Society of Regional Anesthesia and Pain Medicine along with American Academy of Pain Medicine and American Society of Anesthesiologists [44].

1. Ideally treatment session should be carried out in inpatient settings under the care of anesthesiologists, nurse anesthetists, or emergency physicians experienced in ketamine administration and trained in advanced cardiac life support. Availability of personnel and equipment for resuscitation at all times is mandatory (Grade A recommendation).
2. There is a grade B recommendation for the use of ketamine infusion for (CRPS) and Grade D recommendation against fibromyalgia, ischemic limb pain, migraine headache, and low back pain.
3. There is moderate evidence to support the use of higher dosage of ketamine over longer periods for chronic pain conditions.
4. Prior to infusion of ketamine base line ECG should be considered for individuals at high risk of cardiovascular events. Baseline and post infusion liver function tests should be considered for individuals with baseline liver dysfunction



(alcohol abusers, chronic hepatitis) or for patients who also are expected to receive high doses of ketamine at frequent intervals (Grade C evidence).

5. Ketamine should not be used in patients with poorly controlled cardiovascular disease and poorly controlled psychosis (Grade B). It should be avoided in patients with severe hepatic impairment, but may be administered judiciously with proper monitoring in patients with moderate disease (Grade C). Basic monitoring such as hemodynamic and respiratory parameters, sedation levels using a validated scale same as individuals receiving ketamine in a non-chronic treatment regime irrespective of the dose and route of administration are essential.
6. There is limited direct evidence to support the preemptive use of benzodiazepines and  $\alpha 2$  agonists, and there is no evidence to support antidepressant, antihistaminic, or anticholinergic medications prior to start of ketamine infusion at sub-anesthetic doses for CP treatment.
7. There is moderate evidence to support intranasal ketamine for breakthrough pain and low-level evidence for use of oral ketamine and other NMDA antagonists as follow-up therapy after infusion.
8. Given the refractory nature of patients who receive ketamine infusion, the positive outcome could be considered as 30% pain relief or greater in conjunction with patient satisfaction and/or more objective indicators of meaningful benefit such as 12.8% improvement in Oswestry disability index score in a patient with back pain or 20% or greater reduction in opioid use.

## **5. Ketamine in complex regional pain syndrome**

Complex regional pain syndrome (CRPS) was recognized as a distinct pain condition during American civil war in 1864 by Mitchell [45], and it had been described by various names since that time.

It is a chronic pain condition characterized by autonomic and inflammatory features, and it is most often followed by fracture, soft tissue injury, or any surgical procedure, which is often disproportionate in magnitude or duration to the normal course of pain after similar tissue trauma. In 10% of the cases, no inciting cause can be identified [46].

CRPS is subdivided into type 1 and type 2 on the basis of absence or presence of major peripheral nerve injury. The diagnostic features are almost similar in both subtypes although there is difference in etiology, which contributes to uncertainty about the role of neuropathic mechanism [46].

Incidence is found to be greater in females compared with males, and many patients recover within a year, but smaller group may progress to CP. Possible contributing mechanisms include peripheral and central sensitization, autonomic changes and sympathetic afferent coupling, inflammatory and immune alterations in higher centers along with genetic and psychological factors [46]. So effective management of chronic form is often difficult. CRPS causes significant morbidity, and 80% of patients with CRPS are severely disabled [47]. So it needs multidisciplinary care aimed at attaining adequate pain relief, functional restoration, and psychological improvement. Many patients are poorly responsive to regular therapeutic approaches, and ketamine has been shown to decrease pain levels in refractory cases of CRPS in several studies.

## **5.1 Effect of topical application of ketamine**

Various routes of application of ketamine for CRPS had been explained in several studies. Topical application of ketamine in inflammatory and neuropathic pain conditions resulted in reduction of pain by downregulation of NMDA,  $\alpha$ -3-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainite receptors [48]. It had been evidenced that application of 10% ketamine cream reduced tactile allodynia and pain scores within 30 min in CRPS patients. Systemic level of ketamine remained undetectable in the study, which suggested the peripherally mediated effect [49]. Another study showed that topical application of ketamine (0.25–1.5%) to the affected areas of limbs relieved pain and swelling in the early dystrophic stage of CRPS 1. This could be due to the local analgesic effect or peripherally mediated NMDA antagonistic effect of ketamine [50, 51].

## **5.2 Effect of epidural ketamine**

Similarly early stage of CRPS was treated with very low dose of epidural ketamine for 10 days in a patient to get prolonged pain relief up to 8 months, which suggested the role of ketamine on NMDA receptors on dorsal horn neurons [52].

## **5.3 Effect of sub-anesthetic infusion of ketamine**

Kirkpatrick in his study found that patients with lower limb CRPS responded better than upper limb CRPS for graded dose of ketamine for 5 days [53]. However, the study on mouse model of CRPS showed that subcutaneous ketamine reduces the nociceptive sensitization better in chronic stage than in acute stage [54].

A randomized controlled trial on 60 CRPS1 patients had shown that duration of disease did not affect the response of ketamine in sub-anesthetic dose. The study group received a continuous sub-anesthetic titrated dose of S(+) ketamine ranging from (1.2–7.2%  $\mu\text{g/kg/m}$ ) for 4.2 days. S(+) ketamine is 2–4 times more potent than racemic ketamine and required less dose for the same analgesic effects with minimal side effects. Recovery is also quicker with S(+) ketamine due to its rapid clearance compared with R(–) ketamine. Median duration of illness was 7.4 years (0.1–31.9 years). ketamine was found to produce significant reduction in pain scores for 10–12 weeks compared with placebo [55].

Pharmacokinetic-pharmacodynamic study on these patients had shown that concentration of ketamine reduced rapidly on the termination of infusion, but analgesic effect outlasts the treatment period by 10 weeks [56]. This is in contrast with the effect of S (+) ketamine in acute experimental pain where the analgesic effect correlates with its plasma concentration [57]. Prolonged effect of sub-anesthetic dose of ketamine could be due to the long-term desensitization of NMDA receptors in spinal cord or restoration of inhibitory sensory control in the brain [58].

Another low-dose ketamine (0.35 mg/kg/min not to exceed 25 mg/h) study on 19 out patients over 4 h for 10 days showed significant reduction (50%) in affective component of pain. Activity watch scores were significantly reduced. Low dose infusion can be done in outpatient basis and is cost-effective also. However, study was stopped halfway by stressing that higher ketamine dose provided much greater pain relief for prolonged period without any complication [59].

This was also suggested by Goldberg, who studied effect of ketamine infusion at two different doses for two different time periods. In his first study with low-dose ketamine for 10 days in 40 CRPS patients, he found significant reduction in pain scores, with increased ability to initiate movement and tendency to decreased autonomic regulation. A total of 36 patients had pain relief for 2 weeks, while eight

patients had pain relief for 12 weeks similar to Sigterman's study [55], but here they have used racemic ketamine [60].

In his second study on 16 patients with moderate-dose ketamine for 5 days, he found significant reduction in pain scores compared with 10 days regime at the end of infusion ( $2.8 \pm 0.65$  vs  $5.4 \pm 0.91$ ). Pain relief experienced on second day of infusion continued to increase over the fifth day of infusion and correlated well with the maximum plasma levels of ketamine and nor-ketamine. Author also suggested the possible role of downstream metabolites in prolonged analgesia. Similar to Sigterman's study, the pain relief extended up to 12 weeks, although in few cases it prolonged up to 6 m. Significant reduction of pain was reported in 10 out of 16 patients [61]. Another study demonstrated longer duration of pain relief after second treatment of ketamine infusion than the first one in CRPS patients [62]. The sustained effect could also be due to antagonistic effect of ketamine on other receptors. The presence and therapeutic significance of single nucleotide polymorphism of the NMDA receptor cannot be overlooked and opens new route for research [61].

#### **5.4 Ketamine coma**

In refractory and generalized CRPS patients, the anesthetic dose of ketamine in range of (3–7 mg/kg/h) produced significant reduction in pain. As ketamine's analgesic potency and duration of clinical effect are dose-dependent, author had evaluated anesthetic dose of ketamine in these refractory patients along with midazolam and clonidine. Significant pain relief was observed at 1, 3, 5, 6 months. Quality of life and ability to perform work are significantly improved in many of the patients at 3 and 6 months. Ten out of 20 patients were completely pain free for 5–11 years, and they had not taken any pain medication further [63]. On the first day of infusion, mobilization of neurogenic edema fluid occurs, later on third day, venous tone returns to the affected extremity [64]. Few patients experienced muscle weakness and weight loss. No neurocognitive adverse effects were observed at 6 weeks after anesthetic infusion of ketamine in another study. It could also be due to reduction in pain and pain medicine uptake [65]. However, in 20% of patients, nosocomial, urinary, and pulmonary complications have occurred. No long-term psychiatric impairments have been seen in any of these 20 CRPS patients [63].

### **6. Effect of ketamine in other pain conditions**

Although there is a grade D recommendation for the use of ketamine in fibromyalgia, cancer pain, ischemic pain, and migraine headache [44], various studies have demonstrated its beneficial effects in alleviating pain in fibromyalgia, phantom limb pain, ischemic limb pain, and headache [66–69].

#### **6.1 Effect of ketamine in fibromyalgia**

Fibromyalgia, a functional pain syndrome, is characterized by widespread musculoskeletal pain, fatigue, sleep abnormality, and somatic hyperalgesia. Mean estimated global prevalence of fibromyalgia is 2.7% with female preponderance. Patients often experience pain from head to toe; cognitive dysfunction and memory deficit are common severe symptoms of fibromyalgia. Autonomic disturbances manifest in all areas of body, which correlate with severity of fibromyalgia. It is associated with many of the features of central sensitization including hyperalgesia, allodynia, and temporal summation [70].



Diffuse pain processing in the brain is altered, and it correlates with fibromyalgic nociplastic pain. Increased substance P in cerebrospinal fluid, decreased  $\mu$  opioid receptor availability along with high level of opioids in cerebrospinal fluid, and reduced levels of noradrenaline, serotonin neurotransmitters are seen compared with healthy individuals [71–73]. It is often difficult to identify the cause of the nociplastic alteration as it may not be caused by single etiology. Evaluation should be holistic including all symptoms experienced by the patients along with aggravating factors and functional capabilities of the patients. Integrated multidisciplinary approach including patient education, fitness, medical management, and psychotherapy is often needed [70].

Sorenson had found that ketamine produced significant reduction in pain scores and increased endurance in fibromyalgia patients compared with morphine and lidocaine [66]. Graven-Nielsen had also demonstrated that ketamine reduced referred pain, temporal summation, and muscular hyperalgesia in fibromyalgia patients [11]. However, Noppers had reported only short-term benefits after (0.5 mg/kg) of S(+) ketamine corresponding to its plasma concentration in 24 fibromyalgia patients. It is in contrast with the prolonged benefits of long-term infusion of ketamine in CRPS patients, which suggested that duration of infusion is critical rather than the dose of ketamine [74]. Other studies had also proved that long-term infusion produces cascade of molecular changes both at spinal and supraspinal sites [58].

This large inter-patient variability in response to ketamine infusion may occur from a dosing effect, duration of treatment, individual differences in metabolic degradation, genetic variation of NMDA receptors [64]. This variability in response was also reported by Rabben in trigeminal neuropathic patients with 0.4 mg/kg of intramuscular ketamine [75]. Another possibility of varied response in patients could be heterogeneity in pathophysiology of fibromyalgia [71]. Guedj had demonstrated distinct brain function single- photo emission computed tomography (SPECT) pattern in responders and non-responders to ketamine [76].

## **6.2 Headache**

In refractory cases of migraine, titrated doses of ketamine had reduced pain severity in acute states [69]. A randomized controlled trial has reported that 25 mg of intranasal ketamine reduced the severity of aura in migraine patients [77]. Combination of ketamine (0.5 mg/kg in 2 h) and magnesium sulfate (3000 mg in 30 min) had demonstrated immediate pain relief in two cluster headache patients. It also produced reduction in pain intensity and attack frequency for up to 6 weeks along with reduction in suicidal tendencies [78]. Previous studies on effectiveness of memantine against refractory migraine had further suggested the role of NMDA antagonists against headache [79].

## **6.3 Visceral pain syndrome**

Preclinical studies on ketamine in rats have shown to reverse sensitization in visceral pain syndromes, which provides a good rationale for using ketamine in irritable bowel syndrome [80, 81]. Non-responding refractory pancreatic pain in a pediatric patient has shown reduction in pain scores and morphine requirement after sub-anesthetic infusion of ketamine [82].

## **6.4 Ischemic limb pain**

Randomized controlled trial on 35 patients with ischemic limb pain had shown that combination of low dose ketamine and opioid produced significant pain

relief compared with opioid alone [68]. Animal studies had shown that ischemia can produce hyperalgesia and allodynia, hence the addition of low-dose ketamine along with opioid produced enhanced analgesic effect in these patients [68]. Ketamine also tends to reduce the pain in vasoocclusive crisis in sickle cell anemia patients [83].

## **7. Adverse effects and adjuvants**

Ketamine is associated with adverse psychomimetic, cardiovascular, and gastrointestinal effects resulting from its action on various receptors [84–86]. Double-blinded randomized controlled trial using midazolam and clonidine as premedication along with low-dose ketamine up to 5.2 µg/kg/min showed no psychomimetic and cardiovascular adverse effects [59]. However, another study calculated number needed to harm; “harm” defined as ketamine-induced psychomimetic adverse effects; where author found that number needed to harm for hallucination to be 21 when ketamine was used alone and number increased to 35 when used in combination with benzodiazepines suggesting that adjuvant may lessen but not eliminate psychomimetic effects [87]. Research is being conducted to develop wearable device to deliver low, non-dissociative dose of ketamine. Studies on animals and ketamine abusers raised the concern of hepatotoxicity and cystitis on prolonged use [88]. In humans, the incidence of hepatotoxicity and cystitis found to be increased with higher and frequent doses of ketamine; however, the liver enzyme levels were back to normal after withdrawing the drug [63].

## **8. Conclusion**

Medicine is an art as well as science, and the evidence-based medicine not only relies on scientific literature but also the judgment of clinician and patient preferences and satisfaction. The use of ketamine infusion for chronic pain is an evolving treatment that shows great promise. Though the consensus guidelines for intravenous use of ketamine for chronic pain advocate the use of ketamine only for complex regional pain syndrome, various other clinical studies suggested its role in other chronic refractory painful conditions. Effect of ketamine on various receptors not only affects the sensory component but also the affective motivational component of pain. It decreases pain scores along with the reduction of analgesic medications, which further improves well-being and the quality of life. However, continuous refinement of treatment protocol is essential along with emphasis on both long-term safety and effectiveness.

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