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Ketamine: Does Life Begin at 40?

The adage "life begins at 40" rarely applies in pharmacotherapy, because new drugs generally make older agents obsolete. Analgesic pharmacotherapy, however, continues to rely strongly upon historical agents such as morphine, aspirin, and local anesthetics. Ketamine is poised to enter this select group of timeless analgesic agents due to growing interest in its effects on the *N*-methyl-D-aspartate (NMDA) receptor channel complex. Yet despite a wealth of recent evidence for the critical role of this receptor in nociceptive synaptic processing, central sensitization, and pathological pain states, clinical research into the use of ketamine in pain medicine—particularly for chronic noncancer pain—remains incomplete. This lack of research is significant in itself. Whether it reflects a lack of confidence in the drug, concerns about adverse effects, stigma from abuse, or practical problems such as routes of administration or off-label use is unclear. This issue of *Pain: Clinical Updates* summarizes the authors' recent reviews of the evidence concerning ketamine's clinical use.[1,2] For conciseness, the present article provides key literature citations only; we refer the reader to these reviews[1,2] to support any unreferenced statements.

Pharmacology

First synthesized in 1963 during the search for the "ideal" anesthetic, ketamine was so named because it is a "keto" derivative of an amine. It has a chiral center in the cyclohexanone ring and thus exists as optical isomers. Compared with the R(–) isomer, the S(+) isomer has a fourfold greater affinity for the NMDA receptor, twice the analgesic potency, and fewer psychomimetic effects.[3]

Ketamine binds to many sites in the central and peripheral nervous systems including nicotinic, muscarinic, opioid, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), kainate, and gamma-aminobutyric acid A ($GABA_A$) receptors.[4,5] Ketamine also inhibits serotonin and dopamine reuptake and downregulates voltage-gated Na^+ and K^+ channel function.[6] Ketamine is useful as a general anesthetic for trauma patients because it preserves sympathetic reflexes that help support blood pressure in patients who have lost blood. Because it does not interfere with respiratory drive, it is also widely used in resource-poor settings where intubation and intraoperative mechanical ventilation are unfeasible. The analgesic action of low, subanesthetic doses of ketamine predominantly derives from its activity-dependent, noncompetitive blockade of the glutaminergic

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NMDA-receptor channel complex, through binding at phencyclidine (PCP) binding sites in the ion channel.[6] Glutamate is the principal excitatory neurotransmitter throughout the central nervous system; it is involved not only in nociceptive processing, but also in higher functions such as perception, learning and memory, and motor coordination. High doses of ketamine given to developing rodents cause central neurodegeneration,[7] which although not seen clinically is still of concern.[8]

In its resting state, the NMDA receptor is inactive and does not participate in synaptic modulation because its ion channel is plugged by magnesium. This plug is dislodged by postsynaptic depolarization or when serine residues on the channel protein are phosphorylated following activation of calcium-dependent intracellular protein kinases. The NMDA receptor's

The analgesic action of low, subanesthetic doses of ketamine predominantly derives from blockade of the NMDA receptor

ion channel must be open or "active" before ketamine can bind to or dissociate from its binding site within the channel. Binding of ketamine to PCP sites within the ion channel decreases the channel's opening time and frequency, thus reducing calcium ion influx and dampening secondary intracellular signaling cascades.

Experimental and clinical evidence indicates that ketamine reduces opioid-induced tolerance and hyperalgesia; however, the mechanisms involved are only partially understood.[9] In rats, postsynaptic scaffolding proteins connect the NMDA receptor to intracellular signalling systems such as nitric oxide synthase. In addition, activation of protein kinase C and tyrosine kinase cascades facilitates the association of the NMDA receptors, scaffolding proteins, and intracellular signaling. It is believed that ketamine decreases the scaffolding proteins' interaction with protein kinases and other signaling systems and thereby reduces central sensitization and opioid tolerance.[10,11]

Ketamine appears more effective against central sensitization and opioid tolerance than as an analgesic per se

The NMDA-receptor-channel complex is activated only by intense synaptic transmission across the second-order neuron and not by routine physiological transmission. Therefore, ketamine might be expected to be more effective to prevent central sensitization from a nociceptive barrage than for acute "physiological" pain. Indeed, meta-analyses of clinical trials indicate that ketamine supplementation of opioids for acute postoperative pain fails to improve analgesia to a clinically significant degree. In contrast, clinical evidence suggests that ketamine does benefit "pathological" pain states such as neuropathic or cancer pain and that it ameliorates opioid tolerance. In other words, ketamine appears more effective as a "central sensitization modulator" (antiallodynic, antihyperalgesic, and opioid tolerance-reversing) rather than as an analgesic per se.

Ketamine is extensively metabolized by the liver's cytochrome P450 system (with a high hepatic extraction ratio and extensive first-pass effect), mostly to norketamine and hydroxynorketamine, which in turn are glucuronidated. Due to its high hepatic extraction and the minimal renal excretion of intact ketamine, ketamine dosing need not be altered in moderate renal or hepatic dysfunction. Norketamine is pharmacologically active (1/3rd–1/10th potency)[12] and contributes to the analgesic effects of oral ketamine.[13]

Ketamine is listed on the World Health Organization's essential drugs list for refractory cancer pain

In clinical pain management, ketamine is most commonly administered as a continuous low-dose intravenous, or subcutaneous, infusion of 0.05–0.2 mg/kg/h. Subcutaneous or intramuscular absorption is slower but still extensive, with approximately 90% bioavailability.[14] A recent study of 25-mg oral or sublingual ketamine lozenges confirmed a bioavailability of 23% for oral administration (peak level 30 minutes) and 32% for sublingual administration (peak level 120 minutes), with equivalent terminal half-lives of 6 hours. The combined bioavailability of ketamine and norketamine (as ketamine equivalents) was approximately 55% for both routes. These data may lead to increased use of these more convenient routes of administration.[14] The discovery of peripheral NMDA receptors has also led to the evaluation of topical ketamine administration.[15]

Role of Ketamine in Acute Pain and Preventive Analgesia

Systemic Administration

Perioperative ketamine, added to opioid analgesia either as a low-dose bolus (0.1 mg/kg) or a parenteral infusion (0.1–0.2 mg/kg/h), reduced pain scores by less than 1 cm on a 10-cm visual analogue scale up to 48 hours after surgery, and delayed the first analgesic request by 16 minutes. Opioid consumption was reduced by approximately 30%, with a reduction in nausea and vomiting but not other opioid-related adverse effects.[16-19] Ketamine was most effective as a continuous, low-dose intravenous infusion, there being no analgesic benefit from adding ketamine to opioid patient-controlled analgesia (PCA).[19]

Specific Operations

Low-dose ketamine improved rehabilitation after total knee arthroplasty, and S(+) ketamine reduced pain and analgesic drug requirements after abdominal surgery but not after major pediatric urological surgery. A continuous low-dose subcutaneous ketamine infusion provided better analgesia,

Low-dose ketamine decreased morphine-resistant pain, reduced dosage requirements in opioid-tolerant patients, decreased hyperalgesia after remifentanil infusion, and reduced hyperalgesia and allodynia along surgical incisions

with improved respiratory function and less sedation, nausea, and vomiting than intermittent subcutaneous morphine injections for treatment of acute pain after musculoskeletal trauma (predominantly femoral fractures). A transdermal ketamine patch, delivering 25 mg over 24 hours, reduced analgesic use

Summary of Evidence on Ketamine Analgesia

Level 1 (Evidence obtained from a systematic review (or meta-analysis) of all the relevant RCTs):

Low-dose perioperative ketamine is opioid sparing, reduces nausea and vomiting, and has minimal side effects.

Ketamine added to opioid PCA provides no additional analgesic benefit.

Ketamine is most effective as a continuous low-dose infusion for acute pain management.

Ketamine has "preventive" but not "preemptive" analgesic effects.

Ketamine is a safe and effective sedative/analgesic for painful procedures, particularly in children.

Level II (Evidence obtained from at least one properly designed RCT)

Ketamine is most effective as an "antihyperalgesic," "antiallodynic," or "tolerance-protective" treatment.

Ketamine is effective as a "rescue analgesic" for acute pain unresponsive to opioids.

Ketamine reduces acute wound hyperalgesia and allodynia.

Ketamine may reduce the incidence of chronic postsurgical pain following laparotomy, thoracotomy, and mastectomy.

Ketamine reduces lower-limb ischemic rest pain, peripheral neuropathic pain, and spinal cord injury pain.

Ketamine improves fibromyalgia symptoms, including tender point count and aerobic endurance.

Intranasal ketamine reduces breakthrough pain of cancer-related and noncancer origin.

Ketamine reduces migraine severity in both acute and prophylactic therapy.

Ketamine does not improve analgesia when used alone or in combination with local anesthetic for peripheral nerve blocks, intra-articular injection, or wound infiltration.

Level III (Evidence obtained from nonrandomized controlled trials)

Ketamine may be effective for refractory cancer pain in terminal stage disease.

Ketamine may reduce severe chronic phantom limb pain.

Level IV (Evidence obtained from case series)

Ketamine improves analgesia in opioid-tolerant patients.

Intranasal ketamine may relieve migraine aura.

Ketamine may be effective in visceral pain based on human experimental models and limited case reports.

At least 50% of patients fail to respond to oral ketamine and experience side effects in the treatment of chronic neuropathic pain.

Long-term ketamine use may be associated with impairment of memory, attention, and judgment.

Source: Adapted from: National Health and Medical Research Council (NHMRC). How to use the evidence: assessment and application of scientific evidence. AusInfo, Canberra, Australia, 2000, p. 8.

after gynecological surgery. Ketamine in doses from 10 to 50 mg produced dose-dependent analgesia after third molar extraction.[20]

Rescue and "Preventive" Analgesia

Low-dose ketamine was effective as a rescue analgesic in patients with acute postoperative pain who were unresponsive to morphine, reduced dosage requirements in opioid-tolerant patients, and decreased hyperalgesia after remifentanil infusion during laparotomy. Low-dose ketamine reduced wound hyperalgesia and allodynia after nephrectomy and laparotomy.

Perioperative ketamine has "preventive" but not "preemptive" effects in the acute postoperative period. The preventive effects of ketamine may reduce the incidence of chronic postsurgical pain after laparotomy, mastectomy, and thoracotomy, but not after radical prostatectomy or total knee replacement surgery. After amputation, ketamine reduced the incidence of persistent phantom limb pain in a cohort study, but not in a subsequent randomized controlled trial (RCT).[21]

Procedural Sedation and Analgesia

Ketamine is safe and effective, with fewer side effects than opioid-based techniques, particularly in children. The

combination of ketamine and midazolam was more effective and had fewer adverse events than fentanyl/midazolam or fentanyl/propofol for fracture reduction in the emergency department.[22] A PCA bolus combining ketamine 10 mg and midazolam 0.5 mg with a 3–5-minute lockout is an effective and safe method of providing analgesia for burn dressings in adults monitored in a ward setting, based on audit data.

Neuraxial and Regional Administration

Commercially available preparations of ketamine contain a potentially neurotoxic preservative and should not be used centrally. Preservative-free solutions of ketamine appear safe for neuraxial administration, although caution is warranted pending more extensive neurotoxicity data.

Ketamine is safe and effective for procedural sedation and analgesia in children, with fewer side effects than opioids

Epidural ketamine improved analgesia and reduced opioid consumption in children with few side effects. However, a single RCT showed that intrathecal ketamine was ineffective either as a sole agent, or in combination with bupivacaine, for postoperative analgesia, and it also significantly increased nausea, vomiting, and dysphoria.

There is ongoing discussion about the relevance of peripheral NMDA receptors. Most trials on the use of ketamine alone or with local anesthesia failed to observe improved analgesia with peripheral neural blockade, intra-articular injection, or wound infiltration; however, a recently published trial on peripheral use of ketamine after circumcision showed analgesic benefits.[23]

Ketamine for Chronic Noncancer Pain

Chronic pain commonly involves central sensitization or neuropathic processes, clinically manifesting as hyperalgesia or allodynia. While ketamine may have an important role due to its effectiveness on the NMDA receptor, clinical data to support this indication are limited. Interestingly, ketamine was not even discussed in a recent meta-analysis of RCTs of long-term treatments for neuropathic pain.[24]

Commercially available preparations of ketamine contain a potentially neurotoxic preservative and should not be given spinally

Neuropathic Pain

Intravenous low-dose ketamine reduced painful peripheral neuropathy in experimental settings, but the response was highly variable and there were significant side effects, particularly sedation and dizziness. It also reduced allodynia associated with chronic post-traumatic neuropathic pain compared with alfentanil or placebo. A systematic review of treatments for postherpetic neuralgia reported that intravenous ketamine was ineffective,[25] although there is evidence of benefit in limited experimental[26] and clinical studies.[27]

Intravenous ketamine reduced spinal cord injury pain, and iontophoretic administration of S(+) ketamine improved quality of life, health status, and in some cases pain scores, in patients with intractable central pain.

Ketamine improved opioid analgesia in refractory cancer pain, but with considerable side effects

In a small dose-finding study and in an "*N* of 1" RCT, 57% of patients treated for chronic neuropathic pain with oral ketamine (up to 100 mg per day) discontinued treatment within 1 week because of lack of effect or intolerable side effects. Only 14% of all patients and 30% of those enrolled in the "*N* of 1" trial arm reported analgesia with oral ketamine at the end of the 4-week trial, with half experiencing significant side effects.

A retrospective review of oral ketamine in 21 patients with chronic neuropathic pain found that 38% were either "nonresponders " or "equivocal" responders, and 42% discontinued treatment because of side effects. Only 14% continued to use ketamine for over 1 year in doses ranging from 100 to 240 mg per day, and one patient was "misusing" the drug.

Ketamine reduced neuropathic pain associated with multiple sclerosis and Guillain Barré syndrome in case reports. Limited data suggest that oral or intramuscular ketamine may reduce orofacial pain, including trigeminal neuralgia. Topical ketamine-amitriptyline cream reduced refractory neuropathic pain and produced high levels of patient satisfaction; however, this finding was not confirmed by a subsequent RCT.

Complex regional pain syndrome may respond to intravenous ketamine infusion, topical ketamine ointment, or epidural infusion. Short-term intravenous or subcutaneous ketamine infusion and long-term oral ketamine reduced chronic stump and phantom limb pain. When compared to morphine, ketamine showed dose-dependent reduction in lower-limb ischemic pain at rest. Recently, a 4-week course of memantine (a weaker NMDA-receptor antagonist than ketamine) was found to decrease phantom limb pain prevalence and severity for at least 6 months following traumatic upper-extremity amputation.[28]

Efficacy in Other Chronic Pain States

Ketamine infusion improved the symptoms of fibromyalgia, with a reduction in somatic and referred pain, hyperalgesia, tender point count, and increased levels of physical endurance.

Ketamine may have an important role in both chronic noncancer and cancer pain, but relevant clinical data are limited

A 30-minute low-dose intravenous infusion of ketamine reduced chronic neck pain in approximately 50% of patients with whiplash-associated disorder, although this result was not significantly different from results obtained with morphine or lidocaine infusions. There was no consistent effect with any of these infusions on experimentally induced pain.

Intrathecal S(+) ketamine improved spinal opioid analgesia and reduced opioid requirements in a patient with chronic back and leg pain secondary to lumbar disk prolapse and failed back surgery.

Intranasal ketamine was safe and effective for the short-term treatment of breakthrough pain in patients with chronic pain of various etiologies, mainly musculoskeletal and cancer pain.[29]

Subcutaneous ketamine injections were effective both as acute and prophylactic therapy for migraine; migraine aura may respond to intranasal ketamine.

Ketamine provided analgesia in human experimental models of visceral pain; however, oral S(+) ketamine did not alter visceral sensation in healthy volunteers undergoing gastric distension. A subcutaneous ketamine infusion proved useful in the management of chronic pancreatic pain, and case reports describe benefit with sublingual ketamine lozenges for exacerbations of chronic abdominal pain and intractable angina pectoris, after other treatments failed.

Role of Ketamine in Cancer Pain

Although ketamine is included on the World Health Organization's essential drugs list for refractory cancer pain, a Cochrane review stated that "the benefits and harms of adding ketamine to strong pain killers such as morphine for relief of cancer pain are not yet established" due to limited data. Administration of subanesthetic doses of ketamine to improve opioid-tolerant cancer pain is termed "burst" therapy. Ketamine improved opioid analgesia in refractory cancer pain, but with considerable side effects. An open-label audit of intravenous "burst" ketamine therapy (100–500 mg/24 hours for 3–5 days) reported improvement in cancer pain for up to 8 weeks in 62% of patients refractory to morphine. Somatic and neuropathic pain responded in most cases. A subsequent audit of 43 patients showed a response rate of 51%, with best results for mucositis, painful bony metastases, and neuropathic pain; however, dose-dependent adverse cognitive effects occurred in 30% of patients. Severe total body hyperalgesia and allodynia have been described after the sudden cessation of a 3-week ketamine infusion for neuropathic cancer pain.

Recreational ketamine abusers had impaired working, episodic, and semantic memory and increased schizotypal and dissociative symptoms up to three days after last use

Sublingual ketamine (25 mg) was effective for breakthrough pain unresponsive to intravenous morphine in patients receiving intrathecal analgesia for cancer pain. Oral ketamine combined with transdermal nitroglycerin decreased opioid consumption and side effects but had no effect on pain scores in patients receiving oral morphine. Seventy-eight percent of patients using oral ketamine reported an improvement in refractory neuropathic cancer pain, but with significant side effects.

The addition of intrathecal ketamine to spinal morphine improved pain scores and reduced opioid requirements in patients with terminal cancer pain. Intractable neuropathic cancer pain was treated successfully with multimodal intrathecal analgesia including S(+) ketamine for up to 3 months with low plasma levels and no side effects.

Adverse Effects

Low-Dose Systemic Ketamine

Meta-analyses demonstrate that the incidence of adverse effects using low-dose systemic ketamine for acute postoperative pain is low, and no different than that observed with an opioid alone.[18] Adverse central effects such as hallucinations, nightmares, and visual disturbances occur in fewer than 10% of patients and usually respond to dose reduction or the addition of a benzodiazepine. Concurrent experimental analgesic and psychometric testing during targeted infusions of ketamine and fentanyl found potentiation of fentanyl analgesia by ketamine doses insufficient to produce sedation.[30]

Ketamine may reduce the incidence of chronic postsurgical or post-traumatic (e.g., phantom limb) pain

Long-Term Effects on Cognition, Memory, and Mood

The effects of long-term (>1 week) therapeutic ketamine are unknown, although data exist in the experimental neurophysiology and addiction medicine literature. On functional magnetic resonance imaging, recreational ketamine abusers show significant upregulation of dopamine D1-receptor activity in the dorsolateral prefrontal cortex, a system critically involved in memory and judgment. Short-term infusion of subanesthetic doses of ketamine in healthy volunteers produced a significant decrease in attention and semantic memory. Ketamine use in recreational abusers produced severe impairment of working, episodic, and semantic memory as well as increased schizotypal and dissociative symptoms for up to 3 days after the last use compared with non-ketamine-using controls, although for obvious reasons the doses involved are not known.[31] The potential for memory impairment should therefore be discussed with all subjects contemplating long-term ketamine administration.

The psychotropic effects of ketamine include a sensation of floating, "out of body" and near-death experiences, distorted perception (including time, space, and morphology/body), hallucinations, and schizophreniform psychosis. Administration of S(+) ketamine for acute pain relief after trauma increased post-traumatic stress disorder symptoms at 1 year compared to racemic ketamine or an opioid.[32]

It is unclear whether long-term ketamine use produces tolerance or dependence; however, case reports describe tolerance without withdrawal symptoms in chronic ketamine abusers. Due to its abuse potential, ketamine has recently been scheduled as a restricted substance in Australia and the United Kingdom.

Conclusions

Despite ketamine's use for four decades to produce general anesthesia at high doses, evidence to guide its use at subanesthetic doses for pain control is limited and in part contradictory. Depending upon the setting and the study design, some papers describe significant benefit and almost as many report limited or no efficacy. At least three meta-analyses for acute pain relief report good data to support its use; however, solid data are sparse concerning its use for chronic noncancer and cancer pain.

Currently available evidence suggests that ketamine's utility is less as an analgesic per se, and more as an antihyperalgesic, antiallodynic, or tolerance-protective agent for pathological pain states such as severe acute pain, opioid tolerance or hyperalgesia, neuropathic pain, cancer pain, or visceral pain. Ketamine may also have preventive analgesia effects and in some cases may reduce the incidence of chronic postsurgical or post-traumatic (e.g., phantom limb) pain. These effects reflect its activity at the NMDA receptor, which is not involved in normal or physiological nociception but is activated by intense or prolonged nociceptive barrages that induce central sensitization and pathological pain. Adequate knowledge to prescribe this drug in a rational, evidence-based manner will require large, high-quality studies that assess both immediate and longer-term outcomes. We must either investigate and delineate the role of this intriguing drug in pain medicine or let it slip quietly into retirement.

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