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Ketamine: an old drug revitalized in pain medicine

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Key points

- Ketamine is an anaesthetic with analgesic properties.
- Perioperative ketamine reduces the incidence of persistent post-surgical pain.
- The anti-hyperalgesic and anti-tolerant properties of ketamine make it an attractive option in managing pain conditions refractory to conventional treatments.
- Ketamine abuse in the community could lead to ketamine-induced uropathy with associated bladder pain.
- The optimal regimen, long-term safety, and efficacy of ketamine in pain management remain to be explored.

Ketamine is an anaesthetic drug with unique properties. Discovered in the 1960s, it is known to produce a dissociative state with sedation, amnesia, and analgesia. It has relatively less respiratory and cardiovascular depressive effects, and as pharyngeal and laryngeal reflexes are preserved, it makes an attractive option in ambulatory and battlefield anaesthesia. However, concerns over ketamine's psychodysleptic effects had caused it to fall out of favour in the 1980s. In the 1990s, there was a renewed interest in ketamine as an adjuvant analgesic, after the discovery of its anti-tolerant and anti-hyperalgesic effects. Currently, ketamine is being actively studied for potential use in acute and chronic pain conditions, especially where pain management is difficult with conventional treatments like opioids.

From nociception to pain experience

Latest neuroscience research reveals that human pain experience actually arises from nociceptive information processing within a dynamic neural framework—the pain neuromatrix. The pain neuromatrix consists of a complex network of interacting neurones within the central and peripheral nervous systems, giving rise to the sensory–discriminative, affective–motivational, and cognitive–evaluative aspects of pain experience. Nociceptive signals from primary afferent neurones arrive at the dorsal horn of the spinal cord, and are transmitted via secondary neurones to the thalamus within the central nervous system. The thalamus acts as a relay centre by making connections with different brain regions such as primary and secondary sensory cortices, limbic system, and hypothalamus. Neurones within the pain neuromatrix express glutaminergic, monoaminergic, and opioid receptors which modulates their neuronal transmission. Endogenous ligands and pharmacological agents acting on these receptors can either augment or dampen nociceptive transmission and hence alter the pain experience.

Unique properties of *N*-methyl-D-aspartate receptor in nociception

The *N*-methyl-D-aspartate (NMDA) receptor is a glutaminergic ionotropic receptor widely distributed in the central and peripheral nervous system. It plays a crucial role in synaptic plasticity, a process which allows activity-dependent facilitation (long-term potentiation) or inhibition (long-term depression) of synaptic transmission. The ion channel of the NMDA receptor is normally plugged by a magnesium ion. Upon membrane depolarization, the magnesium plug is removed, allowing more efficient opening of the ion channel. This results in sustained hyper-excitability of

Table 1 Physiochemical and pharmacokinetic properties of ketamine

Molecular mass	238 g mol^{-1}
pKa	7.5
Bioavailability	Oral 20% I.M. 93% Intranasal 50% Rectal 25%
Plasma binding	10–30%
Volume of distribution	2.3 litre kg^{-1}
Metabolism	Hepatic microsomal system
Metabolites	80% into norketamine (active) 20% into 4-OH-ketamine and 5-OH-ketamine (inactive)
Elimination half-life	2–3 h
Clearance	12–20 ml min^{-1} kg^{-1}
Excretion	Bile and urine

the neurone—a state known as long-term potentiation. Such functional changes are observed in activities like learning, memory, and neural development. It has also been implicated in the development of severe acute pain and progression to chronic pain—by sustained facilitation of nociceptive transmission. At spinal level, NMDA receptor activation leads to development of central sensitization—an augmentation of nociceptive transmission towards higher brain centres.[1] It is also believed to play a role in development of opioid-induced hyperalgesia (OIH), a state where opioid paradoxically worsens pain (Table 1).

Pharmacology of ketamine

The principle pharmacological action of ketamine is NMDA receptor antagonism. It antagonizes the receptor via binding to its phencyclidine site in a non-competitive manner. This interaction is responsible for ketamine's amnesic, analgesic, and neuropsychiatric effects. Given the role of NMDA receptor in nociceptive signalling, it is reasonable to postulate that ketamine possesses analgesic properties. Ketamine also interacts with opioid, AMPA, Kainate, GABA-A, sodium, potassium, monoaminergic, and cholinergic receptors.

Ketamine is commonly available as a racemic mixture (Ketalar®). The S(+)-ketamine isomer, with three times affinity for the PCP site than that of R(–)-ketamine, is also available in some European countries (Ketanesth®). Ketamine is commonly given via parenteral routes (i.v., i.m., and subcutaneously), while other routes like oral, per rectal, transdermal, transmucosal, intranasal, intra-articular, and neuroaxial (intrathecal and epidural) have also been tried. Ketamine is metabolized by the liver to norketamine (with 20–30% analgesic activity of the parent compound) and other inactive metabolites and is excreted in bile and urine.

Anti-hyperalgesic and anti-allodynic properties of ketamine

The key role of NMDA receptor activation in central sensitization implies that ketamine can potentially attenuate the process and its clinical manifestations. Animal studies using diabetic neuropathic rat model were able to show that infusion of ketamine at subanaesthetic dose for 5 days could produce a long-lasting reduction in hyperalgesia, together with improved responsiveness to opioids.[2] In human studies using experimental burns model, ketamine was shown to reduce temporal and spatial measurements of secondary hyperalgesia, and the combination of ketamine and morphine abolished hyperpathia (clinical manifestation of wind-up phenomenon).[3] In clinical studies, both ketamine and alfentanil were able to significantly reduce cold and mechanical hyperalgesia in patients with neuropathic pain.[4] Ketamine was also shown to reduce muscle pain, temporal summation, and referred pain in patients with fibromyalgia, a clinical syndrome where central sensitization is believed to be the underlying mechanism.[5]

Acute pain

A high-quality systemic review showed that perioperative use of ketamine could reduce opioid consumption and time to first analgesic request.[6] Analgesic benefit was observed in painful procedures such as upper abdominal, thoracic, and major orthopaedic surgeries. Analgesic effect was apparent with subanaesthetic doses, and was independent of the type of intraoperative opioid used. There was also less postoperative nausea and vomiting within the ketamine groups, albeit an increase in psychomimetic side-effects. The addition of ketamine to opioid patient-controlled analgesia in patients after thoracotomy showed opioid-sparing effects and improved analgesia, along with improved respiratory outcomes and patient's satisfaction.[7] Beneficial effects among other types of surgery like major orthopaedic and abdominal surgeries are less clear. In opioid-tolerant patients, postoperative continuous ketamine infusion reduced their pain score but not opioid consumption after surgery.[8]

Pre-treatment with i.v. ketamine reduces pain during propofol injection. Ketamine also reduces pain associated with sickle cell crisis. In prehospital settings, ketamine appears to provide safe and effective analgesia for trauma patients. The addition of ketamine to propofol provided better sedation and analgesia for minor procedures in emergency department settings, although there might be dose-dependent adverse effects.[9] The addition of ketamine to opioid analgesics during burns care (e.g. dressings change, turning, and bathing) not only improves sedation and analgesia, but also provides additional benefit in preserving respiratory drive and airway reflexes in non-intubated patients.[10]

Preventive analgesia

Preventive analgesia is defined as 'Post-operative pain and/or analgesic consumption is reduced relative to another treatment, a placebo treatment or no treatment with the effect observed at a point in time beyond the expected duration of action of the intervention (e.g. 5.5 half-lives of the medicine). The intervention may or may not be initiated before surgery'. Studies have shown that perioperative ketamine use for more than 24 h has a modest but statistically significant reduction in the incidence of persistent post-surgical pain at 3 months after operation. Such beneficial effects were observed at 6 months but not 12 months after surgery.[11]

Cancer pain

Pain is often a distressing symptom in both cancer sufferers and survivors, and opioid therapy is considered the mainstay of cancer pain management. The World Health Organization (WHO) analgesic ladder adopts a three-step approach to utilize paracetamol, non-steroidal anti-inflammatory drugs, and opioids in cancer pain management. While it serves as a simple and effective guide in cancer pain management, it is only efficacious in around

two-thirds of cancer pain patients. Ketamine is often considered in management of these refractory cancer pain, although current evidence is insufficient to allow any conclusion on its effectiveness.[12] Small randomized controlled trials (RCTs) were able to show that addition of ketamine improves the effectiveness of morphine. There are also case reports showing effective analgesia in refractory cancer-related neuropathic pain using intrathecal ketamine infusions, even though the safety profile and potential neurotoxicity is not clear.

Chronic non-cancer pain

Persistent nociceptive input can lead to pain sensitization via activation of NMDA receptor. The antagonistic action of ketamine on NMDA receptor makes it an attractive adjuvant analgesic in management of chronic non-cancer pain. In such cases, ketamine is given as subcutaneous infusion over days to weeks within a subanaesthetic dose range. Studies showed that ketamine had a mild to modest analgesic effect in a variety of chronic pain conditions (e.g. neuropathic pain, central pain syndromes, headaches, and temporomandibular joint disorders).[13] It is not known whether the analgesic effects will persist after cessation of therapy. Heterogeneity in studies also precluded any conclusion on the optimal dosing regimen.

In phantom limb pain (PLP), treatment with ketamine showed a trend towards short-term analgesic benefit, although it was associated with dose-dependent adverse effects. There are very limited data to determine whether ketamine use during early post-amputation period could reduce the incidence of PLP. Two small RCTs showed that i.v. ketamine is superior to lidocaine and alfentanil in post-spinal cord injury neuropathic pain. There is also weak evidence supporting efficacy of ketamine in treating complex regional pain syndrome.[9]

OIH and opioid tolerance

OIH refers to a state of nociceptive hypersensitivity caused by exposure to opioids. In OIH, an increase in opioid dose may lead to increase in pain. Such paradoxical phenomenon is observed after acute use of strong opioids like remifentanil, or in patients receiving long-term opioid therapy, and the NMDA receptor is likely to be involved. Clinically, it can be difficult to differentiate from opioid tolerance, where increasing dose of opioid is required to achieve the same clinical effect. Both phenomena could result in rapidly escalating opioid requirement, predisposing patients to potentially life-threatening adverse events, such as opioid-induced ventilatory impairment.

As an NMDA receptor antagonist, ketamine is expected to reduce or oppose the clinical features of OIH, leading to reduced opioid consumption and improved efficacy of long-term opioids. Unfortunately, the limited clinical evidence available showed that ketamine could neither reduce pain score nor opioid consumption in chronic non-cancer pain patients receiving high-dose opioids.[14] Further clinical trials are in progress with specific focus on ketamine's ability to reduce OIH in opioid-tolerant chronic pain patients.

Regional and local use of ketamine

Ketamine has been given neuroaxially and loco-regionally to augment analgesia.

The addition of intrathecal S(+)-ketamine to bupivacaine decreased time to onset of analgesia, improved the spread, but not duration of spinal block for Caesarean section. The same combination provided better early postoperative analgesia in lower limb amputation but did not affect pain outcome at 1 yr. As a sole neuroaxial agent, perioperative epidural ketamine improves pain relief and overall opioid consumption without increasing the incidence of adverse effects. Ketamine given caudally in combination with local anaesthetic provided better and prolonged analgesia in children.[9]

Intranasal ketamine provided rapid onset of analgesia with mild and transient adverse effects; such use provided effective analgesia in emergency and prehospital settings. No analgesic benefit was shown when ketamine was given via topical, perineural, intra-articular, or wound infiltration.[9]

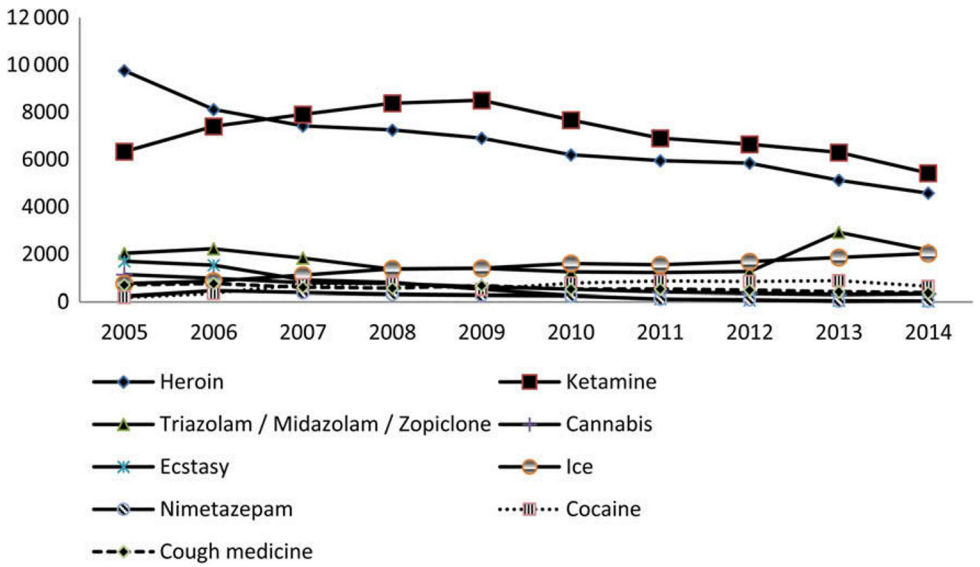

Fig 1 Trend of substance abuse in Hong Kong 2005–2014. There had been an increase in recreational ketamine users since 2005 reaching a peak in 2009. Presentation of ketamine-related chronic bladder pain is probably delayed, as the number of referrals continued to increase, despite a recent decrease in recreational users. (Source of data: Narcotics Division, Security Bureau, The Government of HKSAR, China.)

Adverse effects and abuse potential

Clinical use of ketamine is often limited by dose-dependent side-effects. These include dizziness, sedation, nausea, agitation, hallucinations, and nightmares. Most studies on ketamine in pain management reported short-term results only; information on long-term clinical efficacy and safety are lacking.

Animal studies showed deleterious effects of ketamine on the developing nervous system.[15] There was an increase in the drug's stimulant effects with repeated use of low-dose ketamine in rats. Abnormal histological changes within neural tissues were reported after intrathecal ketamine infusion in canine model.[9] A small study looking at ketamine use for 3 months in neuropathic pain patients reported side-effects such as dizziness, sedation, drowsiness, and dry mouth.[16] In recreational ketamine users, cognitive, hepatic, and urological toxicities were observed. It is worth noting that similar urological toxicity has also been reported in patients receiving analgesic ketamine.[17] In South-east Asia where ketamine is one of the most common abused drugs, we are witnessing an increasing number of ketamine-induced uropathy among ketamine abusers, and many of them present with chronic bladder pain. It is not known whether analgesic ketamine would do further harm to the damaged bladder.

The relationship between chronic pain and problematic drug use is complex, and the problematic use of prescription analgesics is becoming a major healthcare problem in Western countries. For example, in Australia, there has been a 15-fold increase in opioid prescription between 1992 and 2012. Opioid-related hospitalizations have outnumbered those due to heroin poisoning since 2001. Opioid-related death rate has increased from 0.78 to 1.19 deaths per 100 000 population in 10 yr.[18] Given the psychostimulant effects of ketamine, it is susceptible to problematic use akin the opioids. It is advisable to take necessary precautions and regulatory measures before allowing analgesic ketamine to routine practice, especially when oral preparations are being developed for potential out-patient use (Fig. 1).

Conclusion

Ketamine holds promise in becoming one of the armamentarium in fighting acute and chronic pain. Selective use in responders suffering from severe acute or treatment refractory chronic pain may provide improved pain relief, and complements other analgesic modalities. Whether ketamine's analgesic effects will translate into better functional outcomes and facilitate rehabilitation is still unknown. Further research is needed to determine the selection criteria, optimal regimen, and long-term safety profile for routine use of ketamine in acute and chronic pain managements. The recent efforts in developing more selective NMDA receptor antagonists also hold promise in improving the clinical efficacy and safety profile of this group of drugs.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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