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The application of ketamine in pain management for sports injuries and other medical conditions - literature review

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Abstract

Introduction: Ketamine is a well-established dissociative anesthetic. The discovery of its NMDA receptor antagonism revealed new potential applications in pain management. It has demonstrated promise as an analgesic for the treatment of chronic pain and has proven useful in managing acute pain, such as that resulting from sports injuries or in pediatric care settings. It is also a valuable alternative for patients who have not responded well to traditional pain medications.

Materials and methods: This article reviews promising role of ketamine in pain management, especially in chronic or cancer pain, incorporating data from Google Scholar, PubMed, using keywords such as „ketamine”,„chronic pain”, „acute pain”, „pain management”.

Summary: Current evidence supports the use of subanesthetic ketamine as an effective option for acute pain management across various clinical settings, with potential to reduce opioid dependence. Its unique antidepressant properties also make it beneficial for chronic pain patients, especially those with comorbid depression. In conditions like CRPS and sickle cell disease, low-dose ketamine has shown promising results in improving pain and function. However, its effectiveness in fibromyalgia appears limited, with short-term infusions offering only temporary relief. The pediatric population may particularly benefit from ketamine’s rapid, intranasal administration, though dosing and safety must be carefully considered. While early findings are encouraging, more research is needed to establish optimal protocols and to explore its role in managing sport-related injuries.

Conclusions: Ketamine finds various applications in pain therapy and is a promising medication due to its efficacy in both chronic and acute pain management. However, further research is necessary to precisely determine the therapeutic dosage ranges, the long-term effects of its use, and the risk of addiction associated with its administration.
Key words: ketamine, chronic pain, acute pain, pain management

AI: AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

Introduction

Ketamine, originally developed as an anesthetic agent, has gained increasing attention in recent years for its analgesic properties and diverse applications in pain management across various populations, including sportsmen, children, cancer patients, and individuals with chronic pain conditions. As an NMDA receptor antagonist, ketamine plays a critical role in modulating pain pathways, providing effective analgesia while also exhibiting opioid-sparing effects, which is particularly significant in the context of the ongoing opioid crisis[1,2]. Ketamine emerges as a promising adjuvant or alternative therapy in treatment-resistant chronic pain. Its effectiveness in enhancing quality of life for people with complex pain mechanisms which often lead to psychological distress.

One significant advantage of ketamine is the variety of administration routes available, which include intranasal, intravenous, and oral options. This versatility allows for its application in

numerous clinical scenarios. A pertinent example can be found in pediatrics, where the choice of administration route must be tailored to the patient's age. Young children are often resistant to needle pricks; hence, intranasal administration provides a rapid and non-invasive alternative, minimizing additional adverse effects such as pain or distress.

Another application is observed in sports medicine, where medications may need to be administered under challenging circumstances, such as during a match or while climbing. In these situations, it is crucial that the chosen method of delivery is both straightforward and carries a minimal risk of error during administration.

Furthermore, this article will also consider various side effects associated with ketamine use, as they are common with virtually all medications. We will evaluate the overall benefit-risk ratio, emphasizing the advantages that ketamine presents in the context of pain management and other therapeutic areas.

Pharmacological mechanism of action

The pharmacological mechanism of ketamine`s action in managing both acute injuries and chronic pain syndromes in athletes is versatile. It has an analgesic action at many sites both centrally and peripherally.[3] Main analgesic effect occurs through N-methyl-D-aspartate (NMDA). The NMDA receptor is a complex molecular entity which is endowed with a number of distinct recognition sites for endogenous and exogenous ligands. [4] Ketamine acts as an noncompetitive antagonist, interrupting excitatory neurotransmission and attenuating central sensitization processes that contribute to the amplification of pain signals in acute trauma.[5] The antagonism of NMDARs is probably responsible for anaesthetic, analgesia, amnesic and psychosensory effect of ketamine use. [6] According to better understanding of NMDA`s molecular biology, there has been more focus on developing new NMDA receptor blocking drugs, which would help to relieve chronic pain or even central nervous system dysfunction. [7] Ketamine is also known to take part in many other cellular processes such as nicotinic acetyl-choline ion channels, non-NMDA glutamate receptors (a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), delta and mu-opioid agonism and opioid potentiation, metabotropic glutamate receptors (mGluR), L-type Ca2þ channels, the nitric-oxide (NO)ecyclic guanosine-mono-phosphate (cGMP) system, increased release of aminergic neuromodulators (dopamine and noradrenaline)[8] Ketamine also interacts with other receptors, such as opioid and c-aminobutyric acid (GABA) receptors , [6] although in rather high

concentration.

There are reports that ketamine is able to interfere with descending pain inhibitory pathway. [6] It can stimulate noradrenergic neurons, inhibit norepinephrine, serotonin and dopamine uptake. Collectively, these integrated central and peripheral mechanisms underscore ketamine's promise as a versatile analgesic for acute injury management and for the sustained relief of chronic pain in many medicine fields, such as sports medicine.

Acute pain

Ketamine has emerged as a valuable agent in the management of acute pain, particularly within emergency and perioperative settings where rapid and effective analgesia is imperative.

In high doses ketamine is used as a general anesthetic in diagnostic and surgical procedures which do not require skeletal muscle relaxation.[9] Ketamine is also commonly used as a supplement to other anesthetic drugs. However, patients often reported a series of psychotomimetic symptoms when recovering from ketamine-induced anesthesia, including delusions, hallucinations, delirium and confusion, and out-of-body or near-death experiences, which has largely hindered the clinical application of ketamine.[10]

To mitigate these adverse effects, the use of lower, subanesthetic doses has been advocated, as these doses have proven effective in managing acute pain while minimizing the occurrence of psychotropic side effects[11]. Current guidelines suggest that the recommended dose for intravenous ketamine bolus in acute pain management should not exceed 0.35 mg/kg, and continuous infusions should ideally be maintained below 1 mg/kg per hour; nonetheless, pharmacodynamic and pharmacokinetic variances among patients often necessitate further dose adjustments to achieve an optimal balance between analgesia and tolerability. [12] Moreover, emerging evidence supports a promising role for intranasal ketamine as an analgesic modality in emergency scenarios, with randomized clinical trials demonstrating that its efficacy and safety profile is comparable to that of intravenous and intramuscular morphine.[13]

Ketamine is recognized for its analgesic properties while preserving cardiovascular stability, spontaneous respirations, and protective airway reflexes - features that make it particularly advantageous in trauma patients where these physiologic parameters are critical.[14]

The administration of subanesthetic doses of ketamine in acute trauma settings may offer a dual benefit - providing effective sedation and analgesia while simultaneously interfering with the

consolidation of traumatic memories that contribute to the development of stress-related disorders. Traumatic events such as natural disasters, warfare, and severe accidents are known to precipitate conditions including acute stress disorder (ASD) and posttraumatic stress disorder (PTSD), where overgeneral autobiographical memory (OGM) plays a significant role in the persistence and severity of symptoms.[15] Autobiographical memory, comprising both episodic recollections and semantic self-knowledge, serves as a substrate for personal narrative construction; however, when altered by trauma, the resultant OGM leaves affected individuals with less detailed and context-specific memories, a factor implicated in the maintenance of PTSD pathology.[16] Ketamine's mechanism, largely through antagonism of N-methyl-D-aspartate (NMDA) receptors, has been shown to impair the encoding of new episodic memories while leaving the retrieval of previously stored information relatively intact.[17] This selective disruption suggests that by administering ketamine shortly after a traumatic incident, the encoding of the immediate traumatic experience could be modified, potentially inhibiting the development of intrusive memories and related stress disorders. A single subanesthetic injection has been associated with deficits primarily confined to the encoding phase, supporting the hypothesis that ketamine can serve as a neurocognitive intervention that dampens the impact of traumatic experiences without compromising the integrity of pre-trauma autobiographical memory[17]. Moreover, recent evidence from clinical settings indicates that the use of ketamine in prehospital trauma care is associated with a reduced risk of developing PTSD, particularly in patients without traumatic brain injury (TBI). This finding reinforces the proposition that ketamine's effects extend beyond immediate analgesia and sedation to include modulation of the neurobiological processes underlying trauma memory consolidation. In this context, the pharmacological profile of ketamine supports its role not only as an alternative or adjunct to opioid analgesics but also as an agent capable of influencing the subsequent psychological trajectory following acute trauma exposure.[18]

While the evidence is generally supportive, some reviews note that further high-quality, large-scale studies are needed to refine optimal dosing regimens, assess long-term outcomes, and better define its role within multimodal pain management protocols. Despite these limitations, current evidence solidly supports the conclusion that ketamine, particularly at subanesthetic doses, is a useful and effective option in acute pain management across diverse clinical scenarios. Further research is needed to assess ketamine usage in sport-related injuries.

Chronic pain

Ketamine has emerged as a promising agent in the management of chronic pain due to its efficacy in treating both chronic pain and depression, from which both are leading causes of years to disability worldwide. [19]

Chronic pain is subcategorized by the 11th edition of international classification of diseases (ICD-11) into chronic primary pain and chronic secondary pain. Chronic is defined as the pain in one or more anatomical regions that persists or recurs for more than 3 months,and symptoms are not better accounted for by another diagnosis. Chronic secondary pain is considered as a symptom of another condition.[20]

Interest for using ketamine in chronic pain management has led to creation of Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists.[21] According to these recommendations there is a grade B recommendation for the use of ketamine infusion in complex regional pain syndrome, grade D recommendation against fibromyalgia, ischaemic limb pain, migraine headache and lower back pain. According to these recommendations ketamine should not be used in patients with poorly controlled cardiovascular disease and poorly controlled psychosis. It should also be avoided in patients with severe hepatic impairment.

Ketamine as one of N-methyl-D-aspartate (NMDA) antagonists has been receiving new attention in the treatment of neuropathic pain.[22] Neuropathic pain may develop due to damage of the neuron or its downward and upward pathways. Neuropathic pain is often chronic and resistant to therapy with non-steroidal anti-inflammatory drugs and opioids. [23]Systematic review and meta-analysis of 18 randomized control studies in 2022 has shown that there is statistically significant pain reduction by adding ketamine to treatment of chronic neuropathic pain when compared to standard treatment. [24] Although this study revealed also a significant increase in psychedelic effects amongst these patients.

Complex Regional Pain Syndrom

Complex Regional Pain Syndrome (CRPS) is a multifaceted chronic pain condition that typically arises following fractures or soft tissue injury, although it can also occur in the absence of an overt injury.[25] Clinically, CRPS is characterized by severe, persistent pain that is

disproportionate to the initial event, along with a range of sensory, vasomotor, sudomotor, and trophic abnormalities.[26] CRPS is subcategorized into type 1 and type 2. CRPS I is characterized by absence of major peripheral nerve injury, while type II is tied with nerve injury.[27] Population based studies suggest that CRPS occurs in 26 cases per 100 thousand.[28] Incidence is found to be greater in females compared with males.

Research indicates that intravenous ketamine infusions can reduce pain intensity in CRPS patients, with some studies suggesting beneficial effects when used alongside traditional therapies.[29] Recent recommendations suggest that low-dose ketamine infusions can help relieve symptoms of Complex Regional Pain Syndrome (CRPS) and enhance functional recovery, potentially diminishing the need for opioid-based pain relief.[30] Continued investigation is crucial to fully assess the long-term effectiveness and safety profile of ketamine in managing CRPS, as well as to evaluate its role across different therapeutic approaches for the condition.

Fibromyalgia

Fibromyalgia is second most common rheumatic disorder in adult population.[31] It is characterized as a a widespread pain and tenderness in specific areas of the body.[32] It often comes with other symptoms such as sleep disturbances, memory issues and mood disorders like anxiety or depression. The exact cause of fibromyalgia isn't fully understood, but it is believed to involve abnormal pain signaling in the nervous system..[33] The diagnostic criteria for fibromyalgia were originally established in 1990. [34] These criteria made clinical classification standarized, although along with research, there was a necessity to create a newer ones (2010,2011,2016).[35]

In fibromyalgia, both peripheral and central sensitization play key roles in the development and persistence of chronic pain.[36] NMDA receptors play a role in temporal summation of pain from electrical and heat stimuli applied to skin.[37] This increased process observed in fibromyalgia patients might be alleviated through the use of an NMDA receptor antagonist like ketamine. Ketamine has shown promise in managing fibromyalgia symptoms, particularly in cases where conventional treatments have failed, such as gabapentine, [38] milnacipran[39] or oxycodon[40]. Reviews of studies using low-dose ketamine indicate that it can decrease both pain levels and sensitivity to pressure.[41] While the effects can be significant, they are

typically short-lived, and repeated or maintenance infusions may be necessary. [42] In randomized controlled trials the effectiveness of ketamine was short-term due to its pharmacokinetics. The researchers suggest that a brief ketamine infusion does not provide lasting pain relief for individuals with fibromyalgia, indicating that short-term administration may be inadequate for achieving sustained analgesic benefits. [43]

Sickle-cell disease

Sickle-cell disease is one of the most common severe monogenic disorders in the world. [44] Its pathophysiology centers on the polymerization of hemoglobin, leading to rigid, sickle-shaped erythrocytes that obstruct blood flow. This vaso-occlusion results in acute pain episodes and progressive organ damage, affecting the brain, kidneys, lungs, bones, and cardiovascular system.[45] Sickle cell disease (SCD) is linked to early death, with the average lifespan of affected individuals being around 43 years.[46] The application of ketamine in managing vaso-occlusive crises (VOC) in sickle cell disease (SCD) has garnered increasing attention due to its analgesic properties and potential to reduce opioid consumption. Vaso-occlusive crises are the cause of hospitalization in nearly 95% cases. [47] These episodes are characterised by sudden, intense pain, due to tissue ischaemia, caused by sickle-shaped cells occluding blood vessels. Although opioid treatment is often very effective, its usefulness can be limited by unwanted side effects.[48] Recent studies illustrate that low-dose ketamine infusion can facilitate significant pain relief and enhance functional outcomes in these patients.[49] Subdissociative doses of ketamine may reduce the need for opioids, and provide satisfactory analgesia. [29]. Pediatric studies also shown promise, as ketamine seems to be efficient adjuvant to opioid therapy. For instance, retrospective evaluation demonstrated that children receiving ketamine infusions in conjunction with opioids experienced better pain control during VOC compared to those only treated with opioids [50]. Although low doses of subdissociative ketamine seem to be safe for treating vaso-occlusive crises (VOC), there is limited information available on the impact of repeated ketamine use over time.

Acute pain in Pediatrics

Pain is one of the most common complaints during emergency department visits. [51] Acute pain is presented among children with chronic diseases, genetic disorders, juvenile idiopathic arthritis, cancer, inflammatory bowel disease [51]. When it comes to pain management in pediatrics, intranasal route of analgesic administration offers more advantages over the intravenous route ,[52] such as minimizing the possibility of needle-stick injuries, distress to the child by inserting an intravenous cannula or simply providing a faster method[53]. Ketamine in low doses provides analgesia without significant sedation[54], as well as anti-inflammatory effect .[55] Recent studies have demonstrated that ketamine can effectively reduce pain scores in various clinical settings, including postoperative pain management and acute traumatic injuries. One of the analgesics, fentanyl administered intranasally, is known as an effective treatment of acute moderate to severe pain. [33]. There is a study that shows that intranasal ketamine was as effective as intranasal fentanyl for analgesia in children with suspected extremity fractures, highlighting its potential role in emergency scenarios.Ketamine can be administered through several routes, including intravenous infusion, breath-actuated nebulization, and intranasal delivery. Among pediatric populations, the latter two methods—nebulized and intranasal administration—appear to be the most promising due to their non-invasive nature and ease of use. Despite the therapeutic benefits, the implementation of ketamine therapy necessitates careful monitoring and consideration of administration methods, particularly in emergency departments where rapid pain relief is crucial.

Side effects

Ketamine administration, despite being beneficial for various pain management contexts, mentioned above, is associated with different side effects depending on the dosing regimen employed.

Subanesthetic, low-doses (up to 1 mg/kg), generate adverse effects that are generally mild and manageable. Common side effects at this level include lightheadedness, confusion, and short-term hallucinations — commonly known as psychomimetic effects are frequently observed. Although the prevalence of such effects can vary, studies indicate an incidence as low as 0% to 7% in pediatric populations receiving low-dose ketamine [39]. Some studies illustrate that in general population, most frequent side effect observed in patients treated by

subanesthetic ketamine infusion therapy was a feeling of inebriation, in some cases alteration in hepatic enzyme profile was noted.

In contrast, higher doses of ketamine are associated with higher risk of more severe adverse effects. Clinically significant nausea, vomiting and psychotomimetic side - effects were observed in recent studies.At elevated doses, ketamine may induce neurotoxic effects via a mechanism referred to as excitotoxicity. Evidence also indicates that the likelihood of adverse reactions rises with increasing doses of ketamine. In conclusion while ketamine remains an important agent in pain management, attention to dosage is essential to minimize side effects and ensure patient safety.

Summary and conclusions

Current evidence indicates that ketamine, particularly when administered at subanesthetic doses, represents a valuable and effective approach to acute pain management in a variety of clinical contexts. Despite some limitations, the findings underscore its utility across different populations. However, there is a need for additional research to evaluate the application of ketamine specifically in the treatment of sport-related injuries.

Current evidence suggests a promising role for ketamine in the management of acute pain, particularly in the context of addressing the ongoing opioid crisis. In terms of its application in the treatment of chronic pain, an additional advantage is that this condition is often accompanied by comorbid disorders such as depression. Ketamine has been shown to have a positive effect on the treatment of these types of disorders as well. Research indicates that ketamine's rapid antidepressant effects may contribute to improved overall pain management by addressing both pain and its psychological components. While preliminary data suggest that low-dose ketamine could be beneficial in a multimodal approach to CRPS management, further research is necessary to determine the optimal dosing strategies and long-term outcomes for patients. In relation to fibromyalgia, recent findings suggest that a brief ketamine infusion does not yield enduring pain relief for affected individuals, indicating that short-term treatment may not suffice for achieving prolonged analgesic effects. Conversely, recent studies have

demonstrated that low-dose ketamine infusion can significantly alleviate pain and improve functional outcomes in patients with sickle cell disease. Furthermore, administering subdissociative doses of ketamine may lessen the reliance on opioids while providing adequate analgesia for patients in need.When considering the use of ketamine in the pediatric population, it is essential to take into account dosing and potential side effects. However, it appears that ketamine is a promising medication, particularly due to its administration route, which is rapid and intranasal.

Despite some limitations, the findings underscore its utility across different populations. However, there is a need for additional research to evaluate the application of ketamine specifically in the treatment of sport-related injuries.

Disclosure

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