



## Ketamine for the Management of Acute Pain and Agitation in the ICU: Future, Fiction or Just another Drug-Induced Hallucination?

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### Short Communication

Acute pain management is an important consideration in trauma and surgery patients. Inadequate management results in increased in-hospital complications, as well as increased risk of chronic pain and a diminished quality of life [1,2]. Acute pain is the symptom of greatest concern among patients undergoing elective surgery, and according to inpatient hospital surveys, ranks among the top three least desired outcomes [3,4]. In 1996, the American Pain Society (APS) described pain as the “5<sup>th</sup> vital sign” in an effort to emphasize the importance of pain assessment, which led the Veterans Health Administration to incorporate this approach into their national pain management strategy and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to introduce standards which elevated the priority of pain assessment and management (NPC). Opioid-based pharmacotherapy has long been the standard of care for acute pain management in trauma and surgical patients due to a perceived lack of viable alternative therapies, despite the well-known significant adverse effects of these agents, including pruritus, nausea, constipation, ileus, physical and psychological dependence, over-sedation, and life-threatening respiratory depression [5]. Since the implementation of pain as the 5<sup>th</sup> vital sign, opioid prescriptions and opioid-related deaths have quadrupled (CDC) [6,8]. In 2014, approximately two million Americans abused or were dependent on prescription opioids, and approximately 25% of patients who received prescription opioids for chronic non-cancer related pain, struggled with addiction [9]. Opioid addiction is now recognized as a significant public health burden in the United States, prompting the Center for Disease Control and Prevention (CDC) to call for improved opioid prescribing practices. In response to the opioid overdose epidemic, the American Medical Association (AMA) has recently opposed the use of pain as a 5<sup>th</sup> vital sign and has since returned to treating pain as a symptom [6].

In recent years there has been an emphasis on multimodal management of acute pain, specifically the utilization of opioid-sparing adjunct medications, including non-steroidal anti-inflammatories, acetaminophen, gabapentinoids, antiepileptics, tramadol, and regional anesthesia [7]. Additionally, ketamine has been used for the management of acute pain, particularly in patients who have demonstrated an inadequate response to conventional opioid therapy. Ketamine’s mechanism of action, through non-competitive NMDA blockade, enhances the endogenous inhibition of pain perception without causing respiratory depression [10]. Ketamine can also counteract opioid-induced hyperalgesia and prevent the development of opioid tolerance. Previous work demonstrates the safety and utility of ketamine among opioid-tolerant patients undergoing elective operations [11,12].

The forerunner of ketamine, phencyclidine (PCP), was a sedative used in the 1950s and 1960s, but also exhibited analgesic properties distinct from its sedative effects (Perrson). Unfortunately, PCP’s utility was limited by profound dissociative hallucinogenic side effects and was retired clinically [13]. Chemically similar agent with a more favorable side effect profile, gained FDA-approval in 1970 as an anesthetic and sedative. Ketamine’s potential adverse effects include hallucinations, nightmares, and sympathomimetic activity and it is categorized as a schedule III substance due to its low-to-moderate potential for dependence and abuse [14].

According to the American Pain Society Guidelines for the Management of Postoperative Pain, clinicians should consider IV ketamine as a component of multimodal analgesia in adults

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Received Date: 22 Mar 2017

Accepted Date: 30 May 2017

Published Date: 01 Jun 2017

#### Citation:

Peppard WJ, Carver T, DeCleene JH. Ketamine for the Management of Acute Pain and Agitation in the ICU: Future, Fiction or Just another Drug-Induced Hallucination?. *Ann Pharmacol Pharm.* 2017; 2(6): 1059.

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[15]. Ketamine has been associated with decreased post-operative opioid consumption, pain scores, and risk of post-surgical pain [16-20]. Additionally, these guidelines emphasize that clinicians who administer ketamine should be familiar with its use and adverse effects and be able to manage them accordingly. Similar recommendations, provided by the Society of Critical Care Medicine, suggest that non-opioid analgesics be considered to decrease the amount of opioids administered (or to eliminate the need for IV opioids altogether) and to decrease opioid-related adverse effects for non-neuropathic pain [7].

It is important to note that dosing regimens vary widely when prescribing ketamine for its different indications. Much higher doses are used for its sedative indications, such as induction of anesthesia (1-4.5 mg/kg IV push), rapid-sequence intubation (1-2 mg/kg IV push), and procedural sedation (0.5-1 mg/kg IV push) [21]. Neurologic adverse events, including hallucinations, dizziness, feeling of "unreality", and "emergence reactions", are most common with higher doses and IV push administration [21]. At lower doses administered as a continuous IV infusion for pain (typically 2-8 mcg/kg/min), ketamine is well tolerated, although monitoring of vital signs and mental status is still recommended [11,16]. Neurologic adverse effects may still be observed, albeit at a lower incidence, and sympathomimetic effects such as elevations in heart rate and blood pressure are not uncommon; therefore caution is advised when using ketamine in patients with known cardiovascular disease.

A recent Cochrane review concluded that ketamine, administered at a sub-anesthetic dose, is effective in reducing postoperative morphine requirements as well as nausea and vomiting, and that adverse effects are mild or absent [11]. These findings were corroborated by a recent meta-analysis that compared ketamine combined with an opioid patient controlled analgesic (PCA) to an opioid PCA alone [16]. A reduction in postoperative numeric pain scores was realized, both at rest and during mobilization, as well as a reduction in cumulative narcotic consumption, nausea, and vomiting. A recent large, retrospective single center analysis evaluated patients who were on continuous low-dose ketamine for adjunctive analgesia, and concluded that patients receiving continuous ketamine infusions experienced a significant reduction in pain scores compared to traditional opioid-based strategies [17].

We have previously evaluated the role of continuous IV ketamine as an adjunct to opioids for the treatment of acute pain in our trauma/surgical ICU [18]. Our retrospective analysis, comparing data 0-12 hours immediately preceding the initiation of ketamine infusion to data 12-14 hours after the initiation of the infusion, found that the addition of ketamine reduced numeric pain scores (6.54 to 5.37,  $p=0.001$ ), and, more importantly, demonstrated a significant opioid-sparing effect (cumulative morphine 102 mg to 42 mg,  $p=0.001$ ). Unfortunately, adverse effects were not assessed. Based on this study, our group initiated clinical trials evaluating ketamine for acute traumatic rib fracture pain. Currently we have two ongoing prospective, randomized, placebo controlled trials, one in adult patients and the other in elderly patients (NCT02432456). Enrollment is nearly complete, preliminary findings are promising, and results should be published within the year. Future studies at our institution will focus on the management of perioperative pain for other general surgery populations (NCT02785003). We believe that our research will add to the body of evidence supporting the role of ketamine for the management of acute pain, while broadening its indications to

include additional surgical procedures and patient populations.

In the near future we expect to see additional data evaluating the use of ketamine as a sedative in the ICU. Sedation guidelines emphasize the importance of controlling acute pain in critically ill patients, in an effort to spare the use of unnecessary sedative administration [7]. While this approach results in fewer sedative-related adverse effects such as hypotension, delirium, and even potentially increased mortality, the tradeoff is increased analgesic adverse effects, namely from opioids. Ketamine's opioid sparing effect paired with its potentially more favorable adverse effect profile, may offer an advantage by providing both analgesia and sedation in the management of agitation in the ICU. A recent pilot study demonstrated that the frequency of adverse effects associated with ketamine is similar to or lower than that of traditional sedatives [22]. Of note, the dose used for sedation is much higher than that used for pain, though not as high as that used for induction of anesthesia. While the mg/kg dose is similar to that used for RSI, it is thought that because it is administered over an hour, rather than an IV push, it is better tolerated. Given that the adverse effects of ketamine may be dose-dependent, studies must proceed cautiously and take special care to design safe dosing strategies to protect the study patient, and be hyper vigilant in monitoring for adverse events, as safety data are currently lacking for this indication. Only under these circumstances shall the efficacy of ketamine be appropriately evaluated for the management of acute agitation in the ICU. There is no simple solution to curtail the opioid epidemic, but as healthcare providers we must do all that we can to minimize adverse effects associated with opioid prescribing. We must effectively treat acute pain to prevent short and long-term complications, including chronic pain and all its sequelae, while minimizing opioid dependence. To do so we must optimize multimodal therapies that has demonstrated an opioid-sparing effect. In addition to conventional therapy, which includes NSAIDs, APAP, gabapentinoids, anti epileptics, and regional anesthesia, we must continue to explore emerging therapies like ketamine. We must determine the optimal dosing of ketamine to maximize analgesic and sedative benefits and minimize adverse effects, and identify new strategies to avoid unnecessary opioid consumption. This is a good opportunity for physicians and pharmacists to collaborate to optimize currently available therapies and expand their clinical applicability to broader indications.

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