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Ketamine versus hydromorphone patient-controlled analgesia for acute pain in trauma patients

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ABSTRACT

Background: It is unknown whether ketamine administered via patient-controlled analgesia (PCA) provides adequate analgesia while reducing opioid consumption in the traumatically injured patient. Differences in opioid consumption, pain scores, and adverse effects between ketamine and hydromorphone PCA were studied.

Materials and methods: This is an investigator-initiated, single-center, double-blinded, randomized, pilot trial conducted from 2014 to 2016 at a level 1 trauma center. Nonintubated trauma patients in intensive care, who were receiving PCA, were randomized to ketamine or hydromorphone PCA plus opioid analgesics for breakthrough pain.

Results: Twenty subjects were randomized. There was no difference in median daily breakthrough opioid use (10 [0.63-19.38] mg versus 10 [4.38-22.5] mg, $P = 0.55$). Subjects in the ketamine group had lower median cumulative opioid use on therapy day 1 than the hydromorphone group (4.6 [2.5-15] mg versus 41.8 [31.8-50] mg, $P < 0.001$), as well as in the first 48 h (10 [3.3-15] mg versus 48.5 [32.1-67.5] mg, $P < 0.001$) and first 72 h (10 [4.2-15] mg versus 42.5 [31.7-65.2] mg, $P < 0.001$) of therapy. Daily oxygen supplementation requirements were lower in the ketamine group (0.5 [0-1.5] L/min versus 2 [0.5-3] L/min, $P = 0.020$). Hallucinations occurred more frequently in the ketamine group (40% versus 0%, $P = 0.090$).

Conclusions: Ketamine PCA led to lower cumulative opioid consumption and lower oxygen supplementation requirements, though hallucinations occurred more frequently with use of ketamine. Additional studies are needed to investigate the tolerability of ketamine as an alternative to traditional opioid-based PCA.

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Introduction

Opioids administered via continuous infusion, epidural infusion, intermittent intravenous (IV) push or orally, or via patient-controlled analgesia (PCA) device are the preferred analgesia for severely injured patients in the acute phase of care.[1-3] Although opioids provide effective analgesia, untoward effects such as respiratory depression are dose-limiting which may result in the inability to achieve adequate pain relief in some patients.[4] Acute and chronic opioid use has also come under scrutiny related to the current abuse epidemic in the United States as prescription opioid use may lead to increased risk of prescription and illicit drug abuse.[5] The rate of overdose deaths involving opioids has increased by 200% since the year 2000.[6] Prescription opioid and heroin abuse led to a record high death rate due to overdose in 2014, a 14% increase from 2013.[6] Alternative analgesic agents may help patients achieve acceptable pain control and decrease opioid use in the acute post-traumatic and postoperative setting and curtail the need for postacute and chronic opioid therapy.

Ketamine is an N-methyl-D-aspartate antagonist approved for use in induction and maintenance of general anesthesia. Ketamine has also been effective as a primary or adjunctive analgesic agent in postoperative patients.[7-12] Analgesia from ketamine occurs via noncompetitive blockade of glutamate, resulting in modulation of central sensation and hyperalgesia as well as direct activity on kappa, delta, and mu-1 receptors.[13,14] Potential side effects of ketamine include hypertension, tachycardia, hallucinatory effects, and laryngospasm.[7,14] Notably, ketamine lacks the dose-limiting side effects of central nervous system and respiratory depression, key features distinguishing it from opioids.[15] As such, ketamine has gained interest as an alternative or adjunctive analgesic for acute pain management in military and civilian medicine.[16] Ketamine has been studied in PCA devices in combination with opioid agents, but no published studies have evaluated ketamine-only PCA in trauma patients.[9-12]

This pilot study aimed to assess the efficacy of ketamine PCA compared with hydromorphone PCA for baseline analgesia in nonintubated trauma patients with acute pain initially treated in the intensive care unit (ICU). It was hypothesized that ketamine PCA would lead to decreased breakthrough opioid use and similar pain scores compared with hydromorphone PCA in traumatically injured patients.

Methods

Design and oversight

This study was an investigator-initiated, single-center, randomized, patient- and caregiver-blinded, controlled study. The methodology was approved by the University of Cincinnati and the Wright–Patterson Air Force Base Institutional Review Boards. Informed consent was obtained for all subjects at the time of enrollment.

Participants

Nonintubated trauma surgery patients admitted to the surgical ICU were evaluated for inclusion in the study from April 2014 through August 2016. Patients were included if they (i) were adults aged $\geq$ 18 y, (ii) had a total injury severity score[17] of greater than 9, (iii) were planned to receive or were using a PCA for delivery of analgesic therapy, (iv) were able to effectively use a PCA device as assessed by a physician, and (v) had at least one major orthopedic injury, defined as an upper or lower extremity fracture with an Abbreviated Injury Scale of greater than or equal to 2.[17] Due to challenges encountered with a low number of patients meeting these criteria, the inclusion criterion for orthopedic injury was removed 14 mo after the trial commenced. Patients were excluded for (i) body mass index greater than 35 kilograms per meter squared (kg/m^2), (ii) history of bipolar disorder or schizophrenia, (iii) acute kidney injury (defined as serum creatinine increase of 2-3 times baseline or a glomerular filtration rate decrease of greater than 50%),[18] (iv) history of chronic kidney disease, (v) history of liver failure, (vi) history of heart failure or coronary artery disease, (vii) opioid use as outpatient maintenance therapy, (viii) need of treatment of acute withdrawal as indicated by an order for active monitoring of alcohol withdrawal by the treating physician, (ix) Glasgow Coma Scale (GCS) score $<$ 13 or a motor sub-score below six at the time of enrollment, (x) allergy to any medications used in the study (i.e., ketamine, hydromorphone, or lorazepam), (xi) pregnancy, or (xii) actively incarcerated. Cognitive function was assessed for continuation in the study by using the GCS every 6 h. Participants were deemed cognitively impaired and ineligible for continuation if they had a GCS score $<$ 13.

Treatments

Participants underwent randomization to either ketamine or hydromorphone PCA. Randomization was performed using the computerized Wichmann-Hill random number generator in blocks of 10. Participants were assigned to interventions using the random number generator by the local investigational drug services, and study personnel were not involved in randomization or treatment group assignments. Participants, caretakers, and study personnel were blinded to the treatment groups. To maintain blinding, the concentrations of ketamine and hydromorphone in the dispensed PCA syringes were set for the study so that each dosage setting (standard, minimum, or maximum) would deliver the same volume of drug whether the PCA contained ketamine or hydromorphone. Pain scores were measured using the Numeric Rating Scale (NRS) by nurses caring for the subjects who were trained on the use of the NRS. The NRS ranges from 0 to 10, where 0 was no pain and 10 was the worst possible pain.[19] PCA settings allowed for doses of ketamine 1.5-6 mg IV bolus with a lockout of 6 min or hydromorphone 0.1-0.4 mg IV bolus with a lockout of 6 min (Fig. 1). No hourly limits were set, and basal infusions were reserved for subjects with persistent severe pain at highest intermittent dose and PCA mode. Both groups could receive breakthrough opioid analgesia outside of the PCA as hydromorphone 0.5 mg IV push every 2 h as needed for pain scores with NRS of 4-6 or