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Ketamine for Migraine in the Emergency Department

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ABSTRACT
Ketamine is utilized often in the emergency department (ED) for rapid sequence intubation, procedural sedation, and acute pain management. The treatment of migraine headache in the ED varies widely and is dependent on several factors including migraine cause, previous successful abortive methods, and provider preference. Several medications are currently employed to treat acute migraine including nonsteroidal anti-inflammatory drugs, triptans, antihistamines, prochlorperazine, and corticosteroids, among others. Interest in ketamine as an abortive agent to treat migraine has increased as evidenced by recent studies evaluating its use in the ED. This review examines the data regarding the use of ketamine to treat migraine headache. The concept of treating migraine headache with ketamine has been studied for more than 20 years. Early studies conducted primarily in the outpatient setting evaluated ketamine through multiple routes of administration and differing migraine causes with varying results. These early data seem to suggest that ketamine provides relief from headache severity but provides little information regarding the optimal dose and route of administration. Recent active comparator and placebo-controlled trials in the ED utilizing subdissociative doses of ketamine (0.2–0.3 mg/kg intravenously) show conflicting results. To confound the decision regarding its use further, ED providers encounter differing recommendations regarding its place in therapy. Current data suggest that ketamine may provide pain relief to patients with migraine headache. Although there may be a role for ketamine in certain cases after more robust evidence becomes available, currently it is premature to incorporate ketamine into routine use. Several questions remain to be answered including its overall efficacy, place in therapy, dosage, and risk of undesirable side effects. **Key words:** headache, ketamine, migraine, neurology, NMDA receptor antagonist

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A 38-YEAR-OLD female patient with a history of migraine presented to the emergency department (ED) with

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what she reported to be her typical migraine headache, rating her pain at 10/10, and accompanying photosensitivity for 36 hr. She had tried oral acetaminophen, oral ibuprofen, and oral sumatriptan, with no relief. She denied recent falls, invasive procedures, or outpatient medication changes. An ED advanced practice registered nurse (APRN), accompanied by an APRN student, registered to care for this patient. The APRN's assessment revealed an appropriate female patient in moderate distress. The location of her pain was unilateral along the right hemisphere. Vital signs were as follows: heart rate, 74 beats per minute; blood pressure, 138/72 mmHg; respiratory rate, 16 breaths per minute; oral temperature, 36.7 °C (98.1 °F); and a measured weight of 82 kg. The initial impression appeared consistent with migraine headache without aura. The APRN and the APRN student returned to their work area to discuss how to optimally treat the patient. As the conversation evolved, the APRN student inquired about utilizing intravenous ketamine to treat the patient's presumed migraine headache after commenting that he saw some data for its use in migraine.

INTRODUCTION

Ketamine, a phencyclidine derivative anesthetic with *N*-methyl-D-aspartate (NMDA) receptor antagonist properties, is familiar to providers in emergency medicine, anesthesia, surgery, and prehospital medicine. Interest surrounding the use of ketamine has increased recently. It has been investigated as an opioid-sparing agent in treating pain (Motov et al., 2015), optimizing procedural sedation (Newton & Fitton, 2008), and even treating mood disorders (Sanacora et al., 2017). Compelling evidence exists for each of these indications; however, ketamine is gaining attention for treating migraine, an indication for which the supporting evidence is less clear. This review describes the historical and recent data surrounding ketamine as an abortive migraine agent in adult patients.

PHARMACOLOGY OF KETAMINE

Ketamine exhibits its analgesic effects primarily through noncompetitive NMDA antagonism, leading to a reduction in hyperexcitability of the spinal cord and a decrease in pain sensations within the brain. In addition, ketamine has been found to affect opioid receptors in animal models. This less defined mechanism may play an additional role in the analgesic effects of ketamine (Radvansky et al., 2015). Ketamine is currently available in the United States only as a racemic mixture of both S-ketamine and R-ketamine. The S-ketamine isomer is primarily responsible for the NMDA effects as it is more potent than the R-ketamine isomer. Because of increased potency, the use of S-ketamine alone may allow at lower doses for the treatment of pain in comparison with the racemic mixture (Fanta, Kinnunen, Backman, & Kalso, 2015). Although ketamine primarily works via NMDA antagonism, in animal studies, ketamine has been shown to interact with dopamine D_2, serotonin (5-HT), cholinergic, nicotinic and muscarinic receptors, and sodium channel blockers (Peltoniemi, Hagelberg, Olkkola, & Saari, 2016). The interactions with these receptors may be responsible for several of the effects of ketamine from an adverse effects profile. At subdissociative doses (less than 0.3 mg/kg), ketamine is generally well-tolerated by patients. The most common adverse effects include psychomimetic effects, feelings of dysphoria, lightheadedness, nausea, dizziness, and drowsiness (Radvansky et al., 2015).

LITERATURE REVIEW

The hypothesis that ketamine may treat migraine is not a novel theory. Lauritzen and Hansen (1992) demonstrated a compound with NMDA antagonist properties that halted cortical spreading depression in a rat model. Previously thought to be the result of cerebral vasodilation, current migraine abortive therapies now target this pathway. The use of ketamine for pain is largely limited to

intravenous, intramuscular, and intranasal administration due to the poor bioavailability of oral ketamine as described by Radvansky et al. (2015). Therefore, the vast majority of literature for the use of ketamine to treat migraine describes one of these three delivery mechanisms. Ketamine has been investigated as an abortive therapy since 1995 when ketamine 80 mcg/kg subcutaneously provided relief compared with placebo when used to treat acute attacks. In a separate sample of 17 patients with chronic migraines refractory to their home migraine prevention regimens, the addition of ketamine to their prophylaxis regimens (80 mcg/kg subcutaneously three times daily for 3 weeks) was superior to placebo (Nicolodi & Sicuteri, 1995).

Krusz, Cagle, and Hall (2008a) described another study of nine outpatients treated with ketamine 0.45 mg/kg intramuscularly as three separate injections (each 0.15 mg/kg) administered 10 min apart with optional redosing if no adverse effects were reported. Pain severity decreased from 8.65 to 2.71 ($p < 0.001$). Transient dysphoria was observed in four patients. Although these results are significant, the dosing regimen itself may be too cumbersome for use in the ED.

Intranasal delivery of 25 mg of ketamine was studied in patients with migraine aura and a history of familial hemiplegic migraine. With the exception of the first treatment that was administered under medical supervision, patients self-treated their migraine attacks in the outpatient setting. In total, 11 patients were treated, with five reporting alleviation in aura symptoms and a desire to continue the study drug (Kaube, Herzog, Kaufer, Dichgans, & Diener, 2020). It is difficult to draw conclusions from this study considering its small size, probable variation in administration technique, and selection for patients with a family history of hemiplegic migraine.

Afridi, Giffin, Kaube, and Goadsby (2013) reassessed the intranasal route of ketamine under more rigorous conditions. Thirty patients were randomized in a double-blind fashion to receive either 25 mg of intranasal ketamine or 2 mg of intranasal midazolam. Patients with a history of prolonged aura were recruited and allowed to continue their individual migraine prophylaxis regimens. Administration methods and follow-up were similar to the previous study. A scale was developed by the authors to grade aura severity. Complete data were analyzed for 18 patients; baseline median migraine aura duration was longer for the ketamine group than for the midazolam group (30 vs. 13 hr), but aura severity scale scores were similar. Both ketamine and midazolam decreased migraine aura duration by a median of 3 hr, but only the ketamine group showed a statistically significant reduction in aura severity. Data to assess headache relief were incomplete in more than half of patients and were only evaluated in those who did not use any other analgesics. Although an improvement was seen with ketamine in decreasing migraine aura severity, the scale utilized in this study was not validated for external use and the generalizability of its results is unclear.

The first studies investigating intravenous ketamine for migraine did not emerge until 2008. Krusz, Cagle, Hall (2008b) studied 48 infusions of 0.4 mg/kg over 90 min to 30 outpatients with refractory headache. If the infusion was well tolerated, a second dose was administered; however, the time between the doses was not described. Pretreatment severity per the visual analog scale (VAS) was 6.61/10, which was reduced to 3.4 after treatment ($p < 0.001$). The average infusion time was 142 min; however, it is unclear how many patients received more than one infusion. Eight patients were given a third dose, but there were no criteria documented to detail why this was administered. Transient adverse effects were noted in nine patients. An additional case series of six patients aged 8–29 years received a continuous ketamine infusion initiated at a rate of 0.1 mg/kg/hr with titration to maintain a goal pain score of 3/10 or less per VAS for 8 hr. Initial pain scores for all patients were 9–10, and all achieved the goal pain score over an average infusion of 44 hr (range = 12–82 hr). One patient reported dysphoria that resolved upon a

decrease in infusion rate (Lauritsen, Mazuera, Lipton, & Ashina, 2016).

Another study utilizing a similar protocol was conducted wherein 77 inpatient subjects were initiated on a ketamine infusion at 0.1 mg/kg/hr and titrated to a rate of 0.25 mg/kg/hr for 6 hr. Patients were reevaluated for side effects before further dose increases. Pain response, defined as a 2-point decrease in VAS, was achieved in 71.4% of patients. Pain scores improved from admission to discharge (7.1 vs. 3.8, $p < 0.0001$), and patients received continuous ketamine for a mean duration of 4.8 days (range = 2–9 days). Most patients also received additional medications including dihydroergotamine (15.6%), nonsteroidal anti-inflammatory drugs (NSAIDs; 36.3%), and neuroleptics (51.9%) (Pomeroy, Marmura, Nahas, & Viscusi, 2017). Schwenk et al. (2018) recently described their experience administering continuous intravenous ketamine to 61 patients over a mean period of 5.1 ± 0.1 days. The infusions were initiated in most patients at 10 mg/hr to a maximum rate of 1 mg/kg/hr, with a mean maximum infusion rate of 0.76 mg/kg/hr over the study period. Forty-eight patients were considered immediate responders defined as achieving a decrease in pain rating of 2 points on a 10-point numerical rating scale (NRS) from beginning to end of treatment. It should be noted that responders received more intravenous/oral NSAIDs and intravenous/nasal dihydroergotamine than nonresponders. The incidence of adverse effects such as sedation, nausea/vomiting, blurry vision, and hallucinations was similar between responders and nonresponders and considered mild in severity.

Zitek et al. (2018) conducted a dual-center, randomized, double-blind study to assess ketamine 0.3 mg/kg intravenous push and ondansetron 4 mg intravenous push versus prochlorperazine 10 mg intravenous push and diphenhydramine 25 mg intravenous push for the treatment of migraine in 54 ED patients. The primary outcome was reduction in pain according to VAS at 60 min. In the prochlorperazine arm, pain scores improved significantly compared with ketamine (VAS reduction compared with ketamine, 20 mm; 95% CI [2.8, 37.2]; $p = 0.026$]). Unfortunately, the study was terminated early, as some providers believed ketamine was being unmasked as dysphoric reactions were observed in some patients. Two patients in the ketamine group withdrew after experiencing dysphoria. An unplanned interim analysis was performed, and the study was terminated early after observing superiority with prochlorperazine use. Sensitivity analysis to account for dropouts confirmed prochlorperazine superiority. The authors concluded prochlorperazine to be the superior treatment option and that ketamine deserved further study as it did improve pain scores. It should be noted that the outcome of this study may have been influenced had the ketamine been administered as a slow infusion, as recent evidence suggests that administering ketamine as a short infusion over 15 min may decrease the incidence of dysphoria symptoms compared with slow intravenous push (Motov et al., 2017).

Thirty-four adult ED patients with migraine were studied in a placebo-controlled trial evaluating ketamine 0.2 mg/kg intravenous push. There was no difference in pain relief according to NRS reduction at 30 min in the ketamine and placebo arms (between-group median difference interquartile range [IQR] was −1 [IQR = −2 to 1, $p = 0.5035$]). Rescue medication and treatment satisfaction were similar between groups. Incidence of generalized discomfort at 30 min after treatment and fatigue 60 min after treatment were significantly higher in the ketamine group as measured by the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA). The authors concluded that ketamine was well tolerated overall but did not reduce migraine-associated pain more than placebo (Etchison et al., 2017).

Conflicting recommendations exist regarding the place of ketamine in the ED provider's armamentarium. A recent review of benign headache management in the ED suggested that ketamine may be considered a

second-line agent along with propofol and nerve blocks (Long & Koyfman, 2018). In addition, ketamine is gaining favor as an alternative to opioids in the treatment of pain in the ED (Karlow et al., 2018). In contrast, other emergency medicine providers recommend against the extrapolation of increasingly favorable data for ketamine in treating pain as a reason to utilize it as an abortive agent for migraine (Naeem, Schramm, & Friedman, 2018). Furthermore, it is worth mentioning that as ketamine is a known substance of abuse, a risk of dependence or seeking behavior exists as evidenced by reports of high rates (71%) of dependence in long-term (greater than 1 year) recreational users in China (Chen, Lee, & Chan, 2004). Concerns have been raised by Kolar (2018) regarding dependence formation in patients receiving long-term use of ketamine in treating refractory depression, but the relative risk is unknown. There are no data describing drug-seeking or dependent behavior in patients treated with ketamine for pain or migraine.

CONCLUSION

The use of ketamine to treat migraine has been studied for more than 20 years. Until recently, studies evaluating its effectiveness have utilized multiple modes of administration including the intranasal, subcutaneous, intramuscular, continuous, and intermittent intravenous push routes. Outcomes from early trials suggest that ketamine may provide relief from migraine headache, but definitive conclusions are difficult to make, given the variety of dosing methods employed and patient populations studied. Newer studies in the adult ED population utilizing subdissociative intravenous doses (0.2–0.3 mg/kg) continue to suggest that ketamine may provide pain relief; however, there is much yet to be learned regarding its efficacy and safety relative to more proven and established medications. Feelings of dysphoria, at a very low incidence, were reported in studies evaluating ketamine for migraine treatment. Table 1 summarizes current data limitations. At present,

Table 1. Data Limitations Summary

Route	Data limitations summary

Subcutaneous	• Multiple dosing schemes
	  • Acute: 0.08 mg/kg as needed
	  • Chronic migraine prevention: 0.08 mg/kg three times daily for 3 weeks
	• Outpatient setting
	• Small sample sizes (fewer than 20 patients)

Intramuscular	• Multiple Injections • Dosing: 0.15 mg intramuscularly every 15 min for three doses • Small sample sizes (fewer than 20 patients)
Intranasal	• Optimal dose unclear • Outpatient setting • Nonvalidated severity scale utilized, efficacy unclear • Small sample sizes (fewer than 20 patients)

Intravenous	• Outpatient, inpatient, and ED settings
	• Multiple dosing schemes
	  • Continuous infusions (0.11 mg/kg/hr)
	  • Intermittent intravenous push (0.2–0.3 mg/kg)
	• Larger sample sizes (30–77 patients)
	• Adverse effects common

Note. ED = emergency department.

ketamine should not be considered for routine use in cases of acute migraine headache. Until more robust evidence is available, it is reasonable to consider ketamine only in refractory situations with adult patients when other possible causes have been excluded and after consultation with an emergency medicine pharmacist or a physician regarding the unclear benefits and known risks of ketamine. Although beyond the scope of this review, in the event an institution considers implementing ketamine to treat pain in the ED, it is highly recommended to conduct a multidisciplinary approach to generate department guidelines for use including clinical (appropriate patient selection, dosage, administration), operational (storage, preparation, and dispensing of a controlled substance), and safety considerations (need for telemetry monitoring, emergence phenomenon management, and discharge planning).

CASE RESOLUTION

The APRN commended the student for brainstorming alternative therapies. They cautioned that while ketamine is being increasingly studied to treat more conditions, its efficacy and role as an abortive therapy in migraine are not clear yet. For this encounter, the APRN chose to treat the patient's migraine with more proven strategies (fluids, NSAIDs, 5-HT antagonists, antihistamines, and antiemetics) while considering any differential diagnoses.

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