The Journal of Emergency Medicine, Vol. 56, No. 3, pp. 248–257, 2019
Published by Elsevier Inc.
0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2018.12.007

Brief Report

THE THINK (TREATMENT OF HEADACHE WITH INTRANASAL KETAMINE) TRIAL: A RANDOMIZED CONTROLLED TRIAL COMPARING INTRANASAL KETAMINE WITH INTRAVENOUS METOCLOPRAMIDE

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☐ **Abstract—Background: Headache is a common chief complaint in the emergency department (ED) setting. Objectives: To compare analgesia with metoclopramide and diphenhydramine vs. intranasal ketamine among ED patients with primary headache. Methods: We enrolled a convenience sample of adults with a primary headache in a randomized, single-blind, placebo-controlled trial. We randomized patients to either a control arm (intravenous metoclopramide and diphenhydramine) or intranasal ketamine. The primary outcome was change in pain 0–100 mm visual analog scale (VAS) score measured at study start and 30 min post completion of initial medication administration. Secondary outcomes included side effects, hospital admission, and return to care within 48–72 h. Results: All 53 enrolled subjects completed the study, 26 of whom were allocated to the control arm and 27 to intranasal ketamine. The mean change in pain VAS score at 30 min post intervention was 22.2 mm in the control arm vs. 29.0 in the intranasal ketamine arm (effect size difference 6.8 mm, 95% confidence interval −5.8–19.4). The incidence of reported side effects was 65.4% in the control arm vs. 66.7% in the ketamine arm. Three patients (11.5%) allocated to the control arm required admission for headache pain control vs. 1 patient (3.7%) in the intranasal ketamine arm. Three (11.5%) additional patients in the control arm returned to the ED within 48–72 h for headache pain vs. none in the ketamine arm. Conclusions: In this small randomized study, intranasal ketamine was not superior to standard therapy among ED patients with primary headache syndromes. Published by Elsevier Inc.**

☐ **Keywords—headache; ketamine; intranasal; emergency department; migraine; primary headache disorder; diphenhydramine; metoclopramide**

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ClinicalTrials.gov Registration Number: NCT03081416.

INTRODUCTION

Ketamine can provide potent analgesia at subdissociative doses. Routes of administration include intramuscular, intravenous, or intranasal (1). The emergency department (ED) literature examining the use of intranasal ketamine has shown efficacy with this agent in treating orthopedic injuries or providing procedural sedation in pediatric patients (2–6). Applications showing promise for intranasal ketamine use in adult

RECEIVED: 15 September 2018; FINAL SUBMISSION RECEIVED: 26 November 2018;
ACCEPTED: 8 December 2018

patients include treatment of breakthrough of chronic pain, renal colic, and major depressive disorder (7–9).

Headache is a common chief complaint among patients presenting to the ED, accounting for up to 4.5% of ED visits (10). Many of these patients suffer from a primary headache disorder requiring only symptomatic management (11,12). Most primary headache regimens administered in the ED include antiemetic dopamine-antagonists, nonsteroidal antiinflammatory drugs (NSAIDs), and corticosteroids (13–20). Unfortunately, many patients have symptoms that are refractory or recur despite these common treatments (12).

Ketamine is an appealing candidate for an agent to treat headache pain given rapid onset and ability to administer without intravenous access. As with all medications, ketamine carries the risk of adverse side effects to include laryngospasm and prolonged emergence phenomenon. Nevertheless, ketamine has a generally excellent safety profile for ED use to include preservation of respiratory drive and minimal depression of hemodynamic status (1). A single previous study compared the use of intranasal ketamine with intranasal midazolam by patients diagnosed with migraine headaches with prolonged aura in both the inpatient and outpatient settings. This study found that intranasal ketamine provided superior reduction of migraine severity, although with no impact on aura duration (21). The generalizability of these findings to the ED setting remains unclear. The relative pain relief achievable by intranasal ketamine as compared with the aforementioned medications commonly used to treat primary headache in the ED is similarly unknown.

The goal of this study is to compare pain relief with a control arm comprising intravenous metoclopramide and diphenhydramine vs. intranasal ketamine among patients presenting to the ED with primary headache. We hypothesized that intranasal ketamine would lead to superior analgesia compared with the control arm.

MATERIALS AND METHODS

Study Design

We conducted a single-blind randomized controlled superiority trial. The hospital institutional review board approved the study. We conducted the study and reported our results in accordance with the Consolidated Standards of Reporting Trials (CONSORT) Statement (22). We registered the study on clinicaltrials.gov (NCT03081416).

Study Setting and Population

The study setting was an urban tertiary care academic hospital. The annual ED census was approximately 83,000 patients during the study period. Nursing staff identified a convenience sample of potential study subjects presenting to the ED during periods when study investigators were present for enrollment. Periods when the investigators were available for patient recruitment included daytime, nighttime, and weekend hours. Triage nurses notified investigators upon the arrival of patients with a chief complaint of headache. Investigators then approached these patients to screen for inclusion and exclusion criteria after arrival to an ED treatment bed and initial evaluation by the patient's treating provider.

Inclusion criteria included adults (aged 18–65 years) presenting to the ED with a chief complaint of headache, with self-reported severity of 5 or greater on a verbal numeric response scale (0–10). Study eligibility criteria further required that each patient's treating provider believed the headache symptoms to be due to a primary headache syndrome and of sufficient severity to require parenteral analgesia. We intentionally avoided restricting analysis to patients with more specific headache syndromes. By including all patients with primary headache syndromes, our intent was to produce study results applicable to the clinical practice of emergency medicine in which providers may frequently be uncertain as to the specific headache syndrome experienced by any given patient.

Exclusion criteria included weight < 45 kg or > 115 kg given institutional review board and pharmacy concerns that intranasal medications volumes outside of this range would lead to significant variations in medication absorption solely due to differential surface area contact with nasal mucosa. We further excluded patients with altered mental status, focal neurological deficit, or history of psychiatric illness given the potential psychoactive nature of ketamine (9). We also excluded patients with vital sign abnormalities including oxygen saturation < 92%, systolic blood pressure < 80 or > 220 mm Hg, heart rate < 50 beats/min or > 150 beats/min, or respiratory rate < 8 or > 30 breaths/min. We excluded patients with a history of allergic reaction to any of the pharmacologic agents under investigation. We also excluded any patient with a history of drug or alcohol abuse, glaucoma, intracranial hypertension, ischemic heart disease, human immunodeficiency virus or immunosuppression, renal disease requiring dialysis, liver disease, poorly controlled thyroid disease, active bleeding, or current use of anticoagulants.

Study Protocol

We obtained written informed consent from each patient. Consent forms disclosed that each patient would undergo randomization to one of two arms: either a control arm (including intravenous metoclopramide and diphenhydramine in normal saline and intranasal normal saline)

or an intervention arm (including intranasal ketamine and intravenous normal saline placebo). Investigators informed all subjects of their right to withdraw from the study at any time. We documented subject study participation in accordance with the CONSORT Statement (Figure 1) (22).

Subjects allocated to the control arm received 2 mL of 5 mg/mL (10 mg) metoclopramide (Hospira, Lakeforest, IL) solution and 0.5 mL of 50 mg/mL (25 mg) diphenhydramine solution (APP Pharmaceuticals, Schaumberg, IL). We added both medications to 1000 mL of normal saline (Baxter, Deerfield, IL), which we then administered via intravenous bolus. At their discretion, for only those subjects allocated to the control arm, treating clinicians could also add to the bag of normal saline 1 mL of 30 mg/mL (30 mg) ketorolac solution (Hospira, Lakeforest, IL), or 2.5 mL of 4 mg/mL (10 mg) dexamethasone solution (Fresenius Kabi, Bad Homburg vo der Hohe, Germany). Subjects in the control arm also inhaled a dose of atomized intranasal saline (0.015 mL/kg, maximum 1.5 mL) via a MAD Nasal™ intranasal mucosal atomization device affixed to a 10-cc syringe (Teleflex Medical Europe Ltd, Westmeath, Ireland). We further offered each of these patients the option to undergo a repeat dose of intranasal medication 30 min after the complete administration of all initial medications (0.005 mL/kg, maximum 0.5 mL).

Subjects allocated to the intranasal ketamine arm received 1000 mL of normal saline in a bag identical to that administered to the control arm for the purpose of subject blinding. Subjects in the intranasal ketamine arm also inhaled a dose of atomized intranasal 50 mg/mL ketamine solution (Hikma Pharmaceuticals, London, United Kingdom) with the option offered to the patients to undergo a repeat dose 30 min after the complete administration of all initial medications. The first dose equaled 0.75 mg/kg (maximum 75 mg), and the second dose equaled 0.25 mg/kg (maximum 25 mg).

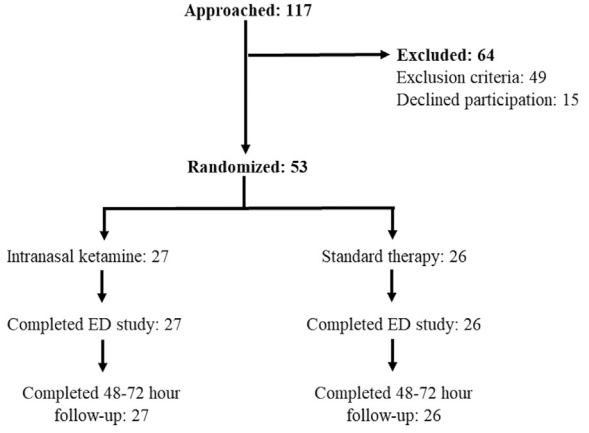


Figure 1. Consolidating standards of reporting trials statement diagram of patient flow. ED = emergency department.

We utilized a computer-generated simple randomization sequence to allocate subjects to each study arm. After screening, consent, and enrollment, we assigned each successive patient a unique subject identification number. We constructed packets for each subject identification number containing sealed envelopes indicating the medications each subject was to receive. These envelopes included dosing tables to assist with preparation of weight-based ketamine and normal saline solutions. Nursing staff responsible for each patient's care opened these envelopes and retrieved and prepared all medications in identical saline bags. Hence, we did not blind nursing staff to the medications received by the patients, though we did blind patients and investigators. Our local protocols and credentialing standards precluded our nursing staff from administering intranasal ketamine. Consequently, treating providers administered all intranasal medications, and for this reason it was not possible to blind treating clinicians to subject arm allocation: treating nurses administered all solutions requiring intravenous administration, and treating clinicians accepted and administered all solutions requiring intranasal administration. Furthermore, treating clinicians required knowledge of the medications to which each patient underwent allocation to guide their decisions for any necessary rescue therapies. Per protocol, we did blind patients and investigators to subject arm allocation.

Fifteen minutes after completion of infusion of all medications, investigators asked each study subject whether he or she would desire an additional dose of the intranasal medication they received earlier. If the subject requested an additional dose, the patient's nurse who prepared the initial study medications would then retrieve the appropriate weight-based dose of the intranasal medication to which the subject underwent allocation. Treating providers administered this second dose at 30 min after the completion of infusion of all medications. We selected this time based upon our belief that this reflected a reasonable time frame over which most clinicians would likely reassess patients for analgesic effect.

At 30 min post completion of medication infusion, we re-evaluated the patient for the purpose of measuring our primary outcome. We did not permit patients to receive rescue therapies outside of those defined above as part of the protocol until after 60 min post completion of medication infusion. All additional medications administered from this time period onward were at the discretion of the treating provider.

Measurements

Investigators collected all data using hard-copy data collection forms. Prior to initial study medication administration, investigators recorded data regarding each

subject's demographics and past medical, surgical, and medication history. Next, investigators instructed subjects to quantify their headache pain using a 100-mm hard-copy visual analog scale (VAS) (23,24). On this scale, 0 mm represented no pain and 100 mm represented the worst pain imaginable. Investigators then solicited repeat pain VAS scores at 15, 30, and 60 min post complete infusion of all initial medications. At the time of ED disposition decision, investigators solicited a 0–10 pain verbal numerical rating scale (VNRS) score with 0 representing no pain and 10 representing the worst pain imaginable. Simultaneously, investigators also solicited a 0–10 satisfaction VNRS score, with 0 representing completely unsatisfied and 10 representing completely satisfied. At the time of each data collection period, investigators also documented the incidence of any adverse events or additional treatment administered by the treatment team.

After the patient left the ED, investigators recorded the times and doses of all medications administered to the patient during the ED stay based upon nursing documentation. During a time window spanning 48–72 h after the patient left the ED, a different investigator, blinded to the arm to which the patient underwent allocation and without any information regarding the patient's ED care, called the patient for study follow-up.

The primary outcome was the change in pain from baseline to 30 min post completion of infusion of initial medications as measured by the 0–100-mm VAS. Secondary outcomes measured during the ED visit included VAS pain score and receipt of rescue medications for analgesia administered at 60 min post medication infusion. We did not consider administration of ketorolac or dexamethasone in the control arm or a single repeat dose of intranasal medication to constitute rescue therapy. Treating clinicians chose the specific rescue medications utilized after the 60-min data collection period as needed for additional analgesia.

Secondary outcomes measured at the time of ED disposition decision included incidence of side effects. For this outcome, we solicited from patients at the time of ED disposition whether they experienced any of the nine side effects measured by the Side Effects Rating Scale for Dissociative Anesthetics. These side effects include fatigue, dizziness, a feeling of unreality, generalized discomfort, nausea, changes in hearing, reduced visual acuity, palpitations, or mood changes (25,26). We did not solicit data regarding severity of individual side effects. We further asked patients to describe any additional unpleasant sensations not otherwise listed in the Side Effects Rating Scale for Dissociative Anesthetics. We did not routinely solicit further data regarding side effects after the time of disposition decision during the patient's index ED visit. Additional outcomes measured at the time of ED disposition included pain VNRS and satisfaction VNRS.

We contacted each subject by telephone at between 48 and 72 h after ED disposition. At that time, we solicited another pain VNRS score. We also solicited whether the patient had returned to a health care provider for additional treatment of their headache symptoms.

Data Analysis

We calculated a sample size estimate for a superiority trial design. Our estimate conservatively assumed a minimal clinically significant difference in pain VAS of 10 mm. This was the lowest difference reported in subgroup analyses by Kelly et al. (23). Our intent in using this value was to ensure adequate power of our study to detect any difference in analgesia between the two study arms. We anticipated a standard deviation in our primary outcome measure of 11.2 (27). Assuming $\alpha = 0.05$ and $\beta = 0.2$ with two-sided testing, we calculated a necessary sample size of 20 subjects in each arm (40 patients total). We conservatively anticipated up to 50% withdrawal prior to measurement of the primary outcome, so requested authorization to recruit 40 subjects in each arm (80 patients total).

We double-entered all hard-copy data collection forms into a password-protected Excel database (version 14; Microsoft, Redmond, WA). We subsequently exported all data into SPSS (version 22; IBM, Armonk, NY) for statistical analysis. We conducted all analyses as intention to treat. We summarized and compared baseline subject characteristics between groups using descriptive statistics with 95% confidence intervals (CIs). We compared the primary outcome between the control and intervention arms by calculating mean effect size difference with 95% CIs with regard to change in pain VAS score from study start to 30 min post completion of administration of initial medications. We compared secondary outcomes of pain and satisfaction VNRS scores between the study arms by calculating differences with confidence intervals using a Hodges-Lehmann estimator (28). Finally, we compared binary secondary outcomes including receipt of rescue analgesia, hospital admission for pain control at index ED visit, and return to a health care provider for analgesia within 48–72 h between the study arms by calculating proportions with 95% CIs.

RESULTS

We approached 117 ED patients for possible inclusion into the study. Of these, we excluded 49 based on our predefined exclusion criteria. Another 15 patients declined to participate in the study. Of the 53 enrolled subjects, 26 underwent randomization to the control arm and the

remaining 27 underwent allocation to the intranasal ketamine arm. All 53 subjects completed the study to include 48–72-h follow-up by telephone (Figure 1). Subject characteristics were similar between the patients allocated to each of the two study groups (Table 1).

Initial mean pain VAS scores were 73.5 mm (standard deviation [SD] 17.5 mm) in the control arm vs. 74.5 mm (SD 16.2 mm) in the intranasal ketamine arm (Table 1). No subjects received additional treatment beyond the medications administered as part of the study prior to measurement of the primary outcome at 30 min post complete administration of initial medications. Among the patients in the control arm, 21 (80.8%) received ketorolac and 7 (26.9%) received dexamethasone in addition to metoclopramide and diphenhydramine. Three (11.5%) patients allocated to the control arm requested and received a second dose of intranasal placebo. Fourteen (51.9%) patients allocated to the ketamine arm requested and received a second dose of intranasal ketamine in accordance with the treatment protocol. Regarding the primary outcome, the mean decreases in pain VAS between initial pain measurements and 30 min after administration of initial medications were 22.2 mm (SD 21.6 mm) and 29.0 mm (SD 24.0 mm), respectively (Table 2, Figure 2). The effect size difference with regards to this outcome was 6.8 mm (95% CI −5.8–19.4 mm). The effect size difference in pain relief between the two arms lessened further in magnitude between completion of administration of initial medications and the 60-min data collection time: 1.5 mm (95% CI −17.8–14.7 mm).

Regarding secondary outcomes, pain VAS scores were comparable between the two study arms through the 60-min data collection period (Supplementary Figure 1, available online). The proportions of patients requiring rescue medication were 30.8% in the control arm vs. 22.2% in the ketamine arm, for an effect size difference of −8.5% (95% CI −33.2–16.1%). Rescue medications administered to patients in the control arm included intravenous ketamine (n = 4), magnesium (n = 4), and opioids (n = 4). We detected no significant differences in any study variables between patients receiving any of these rescue interventions vs. all other subjects in the control arm. Rescue medications administered to patients in the intranasal ketamine arm included intravenous opioids (n = 4), magnesium (n = 3), acetaminophen (n = 3), haloperidol (n = 1), and valproic acid (n = 1). We again detected no significant differences in any study variables between patients receiving any of these rescue interventions vs. all other subjects in the intranasal ketamine arm.

Pain and satisfaction VNRS scores at the time of discharge were both similar between the two study arms. We successfully collected data at 48–72 h for all subjects (Figure 1). Pain VNRS scores 48–72 h after the initial ED visits were similar between the two arms. Three (11.5%) patients allocated to the control arm vs. one patient (3.7%) in the intranasal ketamine arm underwent admission for headache pain control at the index ED visit. Three (11.5%) additional patients allocated to the control arm vs. no patients in the ketamine arm returned to the ED for analgesia related to their headache within 48–72 h (Table 2).

The most common side effects among patients allocated to the control arm included fatigue (53.9%), nausea (42.3%), and dizziness (26.9%). The most common side effects among patients allocated to the ketamine arm included dizziness (33.3%), fatigue (29.6%), changes in mood (25.9%), and nausea (25.9%). The incidence of any side effects was comparable among patients in the control arm (65.4%, 95% CI 44.3–82.8%) vs. ketamine arm (66.7%, 95% CI 46.0%–83.5%, Table 3). No other adverse events occurred during the study.

DISCUSSION

Primary headache disorders are a common cause for ED visits. Achieving effective analgesia in these patients can pose a significant challenge. Typical regimens include antiemetic dopamine-antagonists, NSAIDs, and steroids (13–20). Administration of these regimens generally entails intravenous access. Despite intravenous delivery, some patients experience suboptimal analgesia from

Table 1. Patient Baseline Characteristics

Variables	Control Arm (n = 26)	Intranasal Ketamine Arm (n = 27)
Age, median (IQR), years	31 (25–42)	35 (27–43)
Female sex, %	73.1	66.7
Race, %		
White	73.1	63.0
African American	23.1	25.9
Asian	0.0	3.7
Other	3.8	7.4
Reported history of migraines, %	84.6	81.5
Initial pain score, mean (SD), VAS	73.5 (17.5)	74.5 (16.2)

IQR = interquartile range; SD = standard deviation; VAS = visual analog scale.

Table 2. Patient Outcomes

Variables	Control Arm (n = 26)	Intranasal Ketamine Arm (n = 27)	Effect Size Difference (95% CI)
VAS pain score reduction at 30 min (SD), mean	22.2 (21.6)	29.0 (24.0)	6.8 (−5.8–19.4)
Required rescue medications after 60 minutes (95% CI), %	30.8 (14.3–51.8)	22.2 (8.6–42.3)	−8.5 (−33.2–16.1)
VNRS pain score at discharge, (IQR) median	2 (0–4)	1 (0–4)	0 (−1–1)
VNRS satisfaction score at discharge (IQR), median	9 (8–10)	9 (7–10)	0 (−1–1)
VNRS pain score at 48-72 h (IQR), median	0 (0–0)	0 (0–0)	0 (0–0)
Required admission for headache at index visit (95% CI), %	11.5 (3.2–29.8)*	3.7 (0.0–19.8)†	−7.3 (−22.5–6.9)
Returned to ED within 48–72 hours for headache analgesia (95% CI), %	11.5 (3.2–29.8)‡	0 (0.0–14.8)	−11.5 (−24.1–1.0)

CI = confidence interval; VAS = visual analog scale; SD = standard deviation; VNRS = verbal numerical rating scale; IQR = interquartile range; ED = emergency department.
* Three patients returned to the ED for additional treatment.
† One patient was admitted to the hospital for pain control at the index visit.
‡ None of these 3 patients underwent admission during the index ED visit.

these medications (12). Ketamine offers an intriguing alternative to these regimens given data showing effective analgesia at sub-dissociative doses for other painful conditions, an excellent safety profile, and the capability of intranasal administration, which may obviate the need for intravenous access (1).

The current understanding of the pathophysiology of primary headache disorders provides the basis for studying ketamine as a potential pharmacologic therapeutic agent. Existing pathophysiology theories largely center upon the idea of spreading cortical depression as either an initiating or reactive event (29,30). It is further thought that N-methyl-D-aspartate (NMDA) agonist activity may play a role in these disorders (31,32). Animal studies suggest a role for ketamine in treating this pathophysiologic process (33,34).

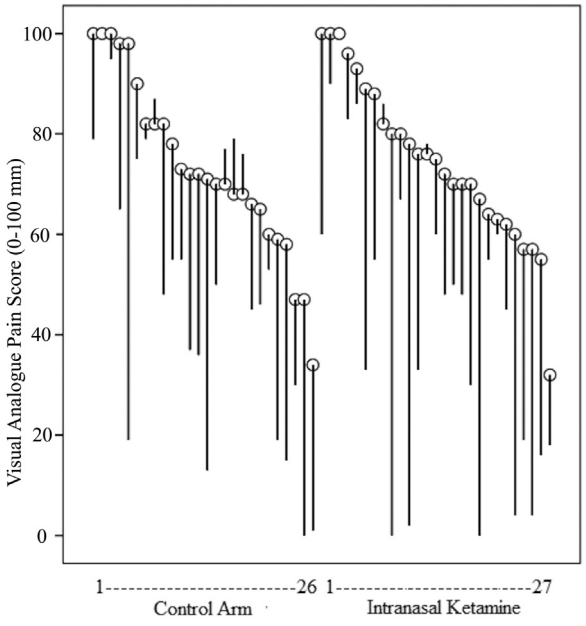


Figure 2. Pain visual analog scale (VAS) scores at baseline and 30 min post intervention. The vertical axes represent mean VAS scores (0 to 100 mm). The horizontal axis separates data for individual subjects. The first 26 data points on the left represent patients allocated to the control arm. The next 27 data points on the right represent patients allocated to the intranasal ketamine arm. Each circle represents the initial VAS score for each patient, and the end of the vertical line represents the VAS at 30 min post intervention.

Our study contributes to a growing literature examining the use of intranasal medications for use in the ED setting. Previous investigations have included studies of the use of inhaled ketamine for analgesia, but also of other agents such as isopropyl alcohol for the treatment of nausea (2,7,8,21,28,35). Nasally inhaled medications are generally attractive for ED use given that administration does not require intravenous line placement, and medication effect onset is generally rapid.

Because we designed our study as a superiority trial, we may only conclude from our results that intranasal ketamine does not achieve superior analgesia compared with standard therapy. However, our results suggest that intranasal ketamine may have comparable analgesia effects to a regimen requiring intravenous access and use of more medications. Indeed, whereas our standard therapy arm only mandated receipt of metoclopramide and diphenhydramine, the vast majority (80.8%) also received ketorolac, suggesting that intranasal ketamine yields similar analgesia compared with the simultaneous use of all three of these agents. A future noninferiority study examining this hypothesis would be a welcome addition to the literature. Notably, a majority of patients allocated to the ketamine arm requested and received a second dose of intranasal ketamine. This finding suggests that the initial dose of 0.75 mg/kg may have provided insufficient analgesia for many patients; future studies might consider examining higher doses.

Our results highlight several additional areas that would benefit from further investigation. First, repeating our study with a consecutive sample would be an

Table 3. Side Effects

Variables	Control Arm (n = 26), % (95% CI)	Intranasal Ketamine Arm (n = 27), % (95% CI)
Fatigue	53.9 (33.4–73.4)	29.6 (13.8–50.2)
Dizziness	26.9 (11.6–47.8)	33.3 (16.5–54.0
Feeling of unreality	0 (0.0–13.2)	18.5 (6.3–38.1)
Discomfort (generalized)	11.5 (2.5–30.2)	11.1 (2.4–29.2)
Nausea	42.3 (23.4–63.1)	25.9 (11.1–46.3)
Changes in hearing	3.9 (0.0–19.6)	0 (0.0–12.8)
Reduced visual acuity	0 (0.0–13.2)	0 (0.0–12.8)
Palpitations	0 (0.0–13.2)	0 (0.0–12.8)
Changes in mood	0 (0.0–13.2)	25.9 (11.1–46.3)
Other	3.9 (0.1–19.6)*	3.7 (0.1–19.0)†
Any side effects	65.4 (44.3–82.8)	66.7 (46.0–83.5)

CI = confidence interval.
* One patient reported auditory hallucinations.
† One patient reported diffuse body paresthesia.

important contribution to minimize the possibility of selection bias that may have affected our study. Our recruitment of a convenience sample may have led to preferential enrollment of patients with less severe headaches, which, in turn, may have led to a patient population more likely to report effective pain relief regardless of intervention. Second, studies examining the combination of intranasal ketamine with conventional medications traditionally used for migraine treatment such as NSAIDs would be interesting to investigate the possibility of synergistic effects of these medications. Third, our study lacked adequate power to demonstrate a difference in rates of hospital admission or return visits for analgesia. Future studies powered to specifically examine these outcomes could illuminate the downstream resource use associated with the alternative migraine treatment strategies. Such studies would ideally include cost-effectiveness estimates (36).

Limitations

This study has several important limitations. First, the subjects comprise a convenience sample. Recruitment occurred when study investigators were available to enroll subjects. Investigator availability included assorted day, evening, and night shifts on all days of the week. However, we did not record dates and times of investigator availability in any systematic fashion. We also did not collect data on the characteristics of headache patients presenting to our ED during times when investigators were unavailable to enroll subjects. Consequently, it is impossible for us to quantify the extent to which selection bias affected our study.

Our study suffers from imperfect blinding. We adopted a single-blind design given our need to rely on treating clinicians to administer intranasal ketamine at our hospital. It was furthermore our anecdotal experience with our patients that nasal inhalation of atomized ketamine may result in a transient bitter olfactory sensation. It is possible that this sensation could have allowed patients to distinguish the study arm to which they underwent allocation. Additionally, patients receiving ketamine frequently develop unique nystagmus patterns. We did not solicit from investigators the arms to which they believed each subject underwent allocation, although it is possible that blinding of investigators was incomplete. Future studies of intranasal ketamine might consider administering poststudy questionnaires to all parties to measure the efficacy of blinding methodologies (35).

We did not collect data regarding time required to administer therapeutic interventions. Although our protocol entailed administration of intravenous medications by bolus, many clinicians are likely to adopt slower infusion rates for many of the conventional migraine medications delivered in the control arm. To the extent that such infusion rates lead to longer lengths of stay, it is possible that our study understates the advantages of intranasal ketamine insofar as intranasal medications obviate the need for intravenous line placement. Furthermore, clinicians may more rapidly deliver such medications compared with intravenous medications. Unfortunately, a related limitation is that we did not collect data on each patient's length of stay. It will be important for future studies to examine this outcome measure in comparing the effects of intranasal medications to treat migraine headaches.

Next, our study afforded each patient's clinician some latitude in medication administration within the protocol. Patients receiving intravenous metoclopramide and diphenhydramine in the control arm could also receive intravenous ketorolac or dexamethasone. Patients receiving intranasal ketamine could receive an additional dose of intranasal ketamine during the study. Our intent with this aspect of the protocol was to better reflect the real-world treatment of primary headache and to build

support for our protocol among our clinicians. However, this came at the expense of difficulties isolating primary outcome effect size attributable solely to a single defined intervention. The relative impact on admissions and return visits by dexamethasone use in our dataset in particular is unclear, given the relatively longer time to onset when compared with the other therapeutic agents.

We did not incorporate procedures to distinguish specific headache syndromes among our included population. This reflected our desire for a pragmatic design that included all ED patients with primary headache syndromes to maximize relevance of the results for ED practice in which it is often not feasible to reliably diagnose the specific headache syndrome afflicting any particular patient. Notably, < 1 in 5 of our included patients in both arms denied a prior history of migraine headaches. To the extent that these self-reported data are accurate, we suspect the vast majority of our patients suffered from migraine headaches. However, this is conjecture, and future study of ED headache management should consider utilizing methodologies to identify specific headache syndrome experienced by subjects for subgroup analyses, as it is likely that some syndromes will have a more or less pronounced response to different headache treatments.

Finally, there are reasons to question the external generalizability of our study. This is due, in part, to the many exclusion criteria defined for purposes of subject enrollment. Furthermore, the study setting was a military hospital whose patient population may not be representative of those in other ED settings. Notably, the VNRS pain scores in both arms at 48–72 h post discharge were 0. In contrast, other ED studies have reported persistence of significant headache symptoms in substantial proportions of ED patients ranging from 31–45% (12,37).

CONCLUSIONS

In this small randomized study, we conclude that intranasal ketamine was not superior to standard therapy among ED patients with primary headache syndromes. Future research examining a noninferiority hypothesis would be useful to ascertain whether intranasal ketamine might prove an adequate alternative not requiring intravenous access to provide analgesia to these patients.

REFERENCES

1. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth 1989;36:186–97.
2. Graudins A, Meek R, Egerton-Warburton D, Oakley E, Seith R. The PICHFORK (Pain in Children Fentanyl or Ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries. Ann Emerg Med 2015;65:248–2541.
3. Yeaman F, Oakley E, Meek R, Graudins A. Sub-dissociative dose intranasal ketamine for limb injury pain in children in the emergency department: a pilot study. Emerg Med Australas 2013;25:161–7.
4. Reynolds SL, Bryant KK, Studnek JR, et al. Randomized controlled feasibility trial of intranasal ketamine compared to intranasal fentanyl for analgesia in children with suspected extremity fractures. Acad Emerg Med 2017;24:1430–40.
5. Tsze DS, Steele DW, Machan JT, Akhlaghi F, Linakis JG. Intranasal ketamine for procedural sedation in pediatric laceration repair: a preliminary report. Pediatr Emerg Care 2012;28:767–70.
6. Pandey RK, Bahetwar SK, Saksena AK, Chandra G. A comparative evaluation of drops versus atomized administration of intranasal ketamine for the procedural sedation of young uncooperative pediatric dental patients: a prospective crossover trial. J Clin Pediatr Dent 2011;36:79–84.
7. Carr DB, Goudas LC, Denman WT, et al. Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study. Pain 2004;108:17–27.
8. Farnia MR, Jalali A, Vahidi E, Momeni M, Seyedhosseini J, Saeedi M. Comparison of intranasal ketamine versus IV morphine in reducing pain in patients with renal colic. Am J Emerg Med 2017;35:434–7.
9. Lapidus KA, Levitch CF, Perez AM, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry 2014;76:970–6.
10. Torelli P, Campana V, Cervellin G, Manzoni GC. Management of primary headaches in adult Emergency Departments: a literature review, the Parma ED experience and a therapy flow chart proposal. Neurol Sci 2010;31:545–53.
11. Friedman BW, Grosberg BM. Diagnosis and management of the primary headache disorders in the emergency department setting. Emerg Med Clin North Am 2009;27:71–87. viii.
12. Friedman BW, Hochberg ML, Esses D, et al. Recurrence of primary headache disorders after emergency department discharge: frequency and predictors of poor pain and functional outcomes. Ann Emerg Med 2008;52:696–704.
13. Bigal ME, Bordini CA, Speciali JG. Intravenous chlorpromazine in the emergency department treatment of migraines: a randomized controlled trial. J Emerg Med 2002;23:141–8.
14. Colman I, Brown MD, Innes GD, Grafstein E, Roberts TE, Rowe BH. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. BMJ 2004;329:1369–73.
15. Jones J, Sklar D, Dougherty J, White W. Randomized double-blind trial of intravenous prochlorperazine for the treatment of acute headache. JAMA 1989;261:1174–6.
16. Davis CP, Torre PR, Williams C, et al. Ketorolac versus meperidine-plus-promethazine treatment of migraine headache: evaluations by patients. Am J Emerg Med 1995;13:146–50.
17. Duarte C, Dunaway F, Turner L, Aldag J, Frederick R. Ketorolac versus meperidine and hydroxyzine in the treatment of acute migraine headache: a randomized, prospective, double-blind trial. Ann Emerg Med 1992;21:1116–21.
18. Larkin GL, Prescott JE. A randomized, double-blind, comparative study of the efficacy of ketorolac tromethamine versus meperidine in the treatment of severe migraine. Ann Emerg Med 1992;21:919–24.
19. Colman I, Friedman BW, Brown MD, et al. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. BMJ 2008;336:1359–61.
20. Baden EY, Hunter CJ. Intravenous dexamethasone to prevent the recurrence of benign headache after discharge from the emergency department: a randomized, double-blind, placebo-controlled clinical trial. CJEM 2006;8:393–400.
21. Afridi SK, Giffin NJ, Kaube H, Goadsby PJ. A randomized controlled trial of intranasal ketamine in migraine with prolonged aura. Neurology 2013;80:642–7.
22. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. PLoS Med 2010;7:e1000251.

23. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J 2001;18:205–7.
24. Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med 1998;5:1086–90.
25. Eide PK, Jorum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain 1994;58:347–54.
26. Motov S, Mai M, Pushkar I, et al. A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. Am J Emerg Med 2017;35:1095–100.
27. Aicher B, Peil H, Peil B, Diener HC. Pain measurement: Visual Analogue Scale (VAS) and Verbal Rating Scale (VRS) in clinical trials with OTC analgesics in headache. Cephalalgia 2012;32: 185–97.
28. Beadle KL, Helbling AR, Love SL, April MD, Hunter CJ. Isopropyl alcohol nasal inhalation for nausea in the emergency department: a randomized controlled trial. Ann Emerg Med 2016;68:1–91.
29. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. Brain 1994;117(Pt 1):199–210.
30. Russell MB, Olesen J. A nosographic analysis of the migraine aura in a general population. Brain 1996;119(Pt 2):355–61.
31. Chen X, Shu S, Bayliss DA. HCN1 channel subunits are a molecular substrate for hypnotic actions of ketamine. J Neurosci 2009;29: 600–9.
32. Nicolodi M, Sicuteri F. Exploration of NMDA receptors in migraine: therapeutic and theoretic implications. Int J Clin Pharmacol Res 1995;15:181–9.
33. Rashidy-Pour A, Motaghed-Larijani Z, Bures J. Tolerance to ketamine-induced blockade of cortical spreading depression transfers to MK-801 but not to AP5 in rats. Brain Res 1995;693:64–9.
34. Gorelova NA, Koroleva VI, Amemori T, Pavlik V, Bures J. Ketamine blockade of cortical spreading depression in rats. Electroencephalogr Clin Neurophysiol 1987;66:440–7.
35. April MD, Oliver JJ, Davis WT, et al. Aromatherapy versus oral ondansetron for antiemetic therapy among adult emergency department patients: a randomized controlled trial. Ann Emerg Med 2018;72:184–93.
36. April MD, Murray BP. Cost-effectiveness analysis appraisal and application: an emergency medicine perspective. Acad Emerg Med 2017;24:754–68.
37. Ducharme J, Beveridge RC, Lee JS, Beaulieu S. Emergency management of migraine: is the headache really over? Ann Emerg Med 1998;5:899–905.

ARTICLE SUMMARY

1. Why is this topic important?

Headache is a frequent reason for emergency department (ED) visits, which commonly require the administration of intravenous medications.

2. What does this study attempt to show?

Intranasal ketamine achieves superior analgesia compared with intravenous metoclopramide and diphenhydramine among ED patients with primary headache disorders.

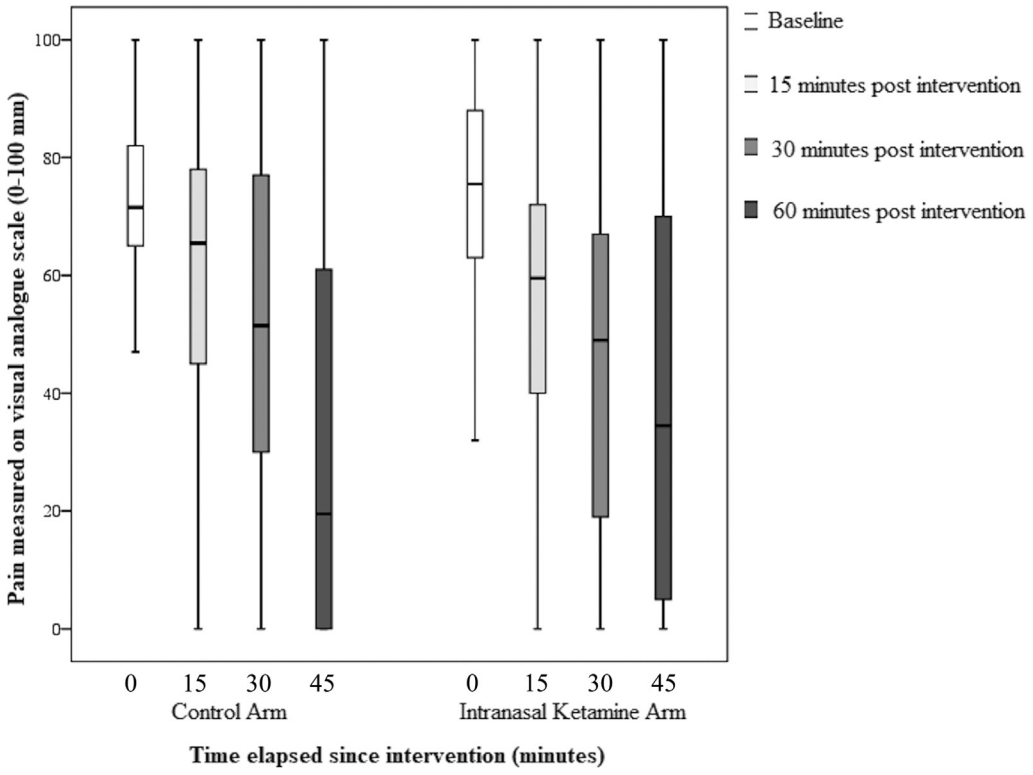
3. What are the key findings?

The mean change in pain visual analog scale score at 30 min post intervention was 22.2 mm in the control arm vs. 29.0 in the intranasal ketamine arm (effect size difference 6.8 mm, 95% confidence interval −5.8–19.4). We hence did not find intranasal ketamine to be superior to the control arm, though analgesia appeared comparable.

4. How is patient care impacted?

Emergency medicine providers can consider use of intranasal ketamine as an effective analgesic not requiring intravenous access among ED patients with primary headache disorders.

Appendix



Supplementary Figure 1. Box plot of pain visual analog scale (VAS) scores at baseline and at 15 min, 30 min, and 60 min post intervention. The vertical axes represent mean VAS scores (0 to 100 mm). The horizontal axis separates data according to time of data measurement, stratified by treatment arm. The left set of box plots represent patients allocated to the control arm. The right set of box plots represent patients allocated to the intranasal ketamine arm.