BRIEF TECHNICAL REPORT

Ketamine for Refractory Headache
A Retrospective Analysis

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Background and Objectives: The burden of chronic headache disorders in the United States is substantial. Some patients are treatment refractory. Ketamine, an *N*-methyl-D-aspartate antagonist, provides potent analgesia in subanesthetic doses in chronic pain, and limited data suggest it may alleviate headache in some patients.

Methods: We performed a retrospective study of 61 patients admitted over 3 years for 5 days of intravenous therapy that included continuous ketamine to determine responder rate and patient and ketamine infusion characteristics. Pain ratings at 2 follow-up visits were recorded. An immediate responder was a patient with decrease of 2 points or greater in the numerical rating scale (0–10) from start to final pain in the hospital. Sustained response at office visits 1 and 2 was determined based on maintaining the 2-point improvement at those visits. Patients were assessed daily for pain and adverse events (AEs).

Results: Forty-eight (77%) of the 61 patients were immediate responders. There were no differences regarding demographics, opioid use, or fibromyalgia between immediate responders and nonresponders. Maximum improvement occurred 4.56 days (mean) into treatment. Sustained response occurred in 40% of patients at visit 1 (mean, 38.1 days) and 39% of patients at visit 2 (mean, 101.3 days). The mean maximum ketamine rate was 65.2 ± 2.8 mg/h (0.76 mg/kg per hour). Ketamine rates did not differ between groups. Adverse events occurred equally in responders and nonresponders and were mild.

Conclusions: Ketamine was associated with short-term analgesia in many refractory headache patients with tolerable adverse events. A prospective study is warranted to confirm this and elucidate responder characteristics.

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Ketamine, a phencyclidine derivative, is a dissociative anesthetic that provides potent analgesia at subanesthetic doses. It is an *N*-methyl-D-aspartate (NMDA) receptor antagonist, which is thought to be the primary mechanism responsible for its analgesic properties. In addition, ketamine acts on opioid, non-NMDA glutamatergic, and muscarinic cholinergic receptors; facilitates γ-aminobutyric acid signaling; and has local anesthetic properties.[1] Subanesthetic ketamine may also be effective for short-term relief of chronic migraine and other refractory headache disorders,[2,3] which affect up to 2% of the population of the United States, inflicting a major clinical and financial burden on patients and the health care system.[4] The mechanism by which ketamine is effective in treating headache pain is not entirely clear. However, memantine,[5,6] magnesium,[7] and amantadine,[8] all NMDA receptor antagonists, may be effective for headache and migraine prophylaxis, which supports the involvement of the NMDA receptor. *N*-methyl-D-aspartate receptor antagonism may decrease chronic pain by inhibiting glutamate-induced neurotoxicity, decreasing central sensitization and specifically in migraines by inhibiting cortical spreading depression.[9] Our clinical experience suggests that there are many patients who experience substantial relief and a smaller group of others who do not benefit from this therapy. We therefore performed a retrospective analysis of patients admitted to our hospital for treatment of refractory headaches over a 3-year period to determine responder rate and patient and ketamine infusion characteristics.

METHODS

After approval by the institutional review board (Thomas Jefferson University, January 16, 2014, Control #14D.552), we conducted a retrospective chart review of 61 consecutive patients from January 2014 through December 2016 admitted to Thomas Jefferson University Hospital for intravenous (IV) treatment of refractory headache with ketamine infusion. All patients with data available were included. Patients who had previously received ketamine for refractory headache were excluded. Patients were admitted to the neurology service in conjunction with the Jefferson Headache Center for aggressive IV therapy, and the acute pain management service (APMS) was consulted for management of IV ketamine for each patient. The APMS consists of a physician-led, nurse-driven team that provides coverage 24 hours per day, 7 days per week, with weekend time being covered by residents. Acute pain management service nurses are permitted to adjust ketamine infusion rates within the context of a protocol, but they do not

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TABLE 1. Demographic Data

Variable	All Patients (n = 61)		
Male/female, n	44/17		
Age, mean (range), y	42.4 (20 – 65)		
Weight, mean (SEM), kg	85.4 (2.7)		
Migraine, n (%)	59 (97)		
Cluster headache, n (%)	2 (3)		
Variable	**Immediate Responders (n = 48)**	**Nonresponders (n = 13)**	***P***
Male patients, n (%)	13 (27)	6 (46)	0.191
Age, mean (SEM), y	43.2 (1.7)	39.2 (3.4)	0.355
Daily opioid use, n (%)	32 (67)	6 (46)	0.570
Fibromyalgia, n (%)	9 (19)	2 (15)	0.781

give bolus doses (Appendix A, Supplemental Digital Content 1, http://links.lww.com/AAP/A257). Admission and scheduling were based on bed availability, and patients were not necessarily experiencing migraine exacerbations on admission. The electronic medical records, daily APMS notes, and the preadmission and postadmission clinic notes from the Jefferson Headache Center were retrieved, and the following data were recorded: name; medical record number; demographics; home medications; diagnosis, based on *International Classification of Headache Disorders, Third Edition*) criteria[10]; pain level on admission and daily pain level during and at the end of hospitalization; ketamine infusion rates and changes during admission; the presence of adverse events (AEs); and medications given to manage AEs. Pain levels from the first 2 office visits after discharge were recorded.

Ketamine infusions were typically started at 10 mg/h for most patients with a few exceptions and titrated up in increments of 5 mg/h every 3 to 4 hours to a soft upper limit of 1 mg/kg of body weight per hour. Adverse events, including hallucinations, delirium, blurry vision, nightmares, nausea, and hypertension, were routinely assessed. These AEs were the primary limiting factor in the rate and degree of titration. Admissions were planned to be 5 days unless a patient could not tolerate the full course of treatment or other factors dictated a longer admission. A clonidine patch was used for management of psychomimetic and sympathomimetic adverse effects. A benzodiazepine was also available as needed for treatment of AEs. Other medications routinely ordered by the headache service included, but were not limited to, prochlorperazine, metoclopramide, methylprednisolone, and ketorolac. In general, home analgesics were continued. Daily opioids were being used for management of other comorbid refractory chronic pain conditions, not for the management of refractory headache. In general, patients were routinely counseled by the outpatient headache providers on the risk of opioid use, including medication overuse headache (MOH). Opioids were being prescribed by nonheadache providers. Patients were encouraged to minimize the daily dose of opioids, and attempts were made to coordinate alternative management of chronic nonheadache pain disorders with other providers.

We predefined an "immediate responder" as a patient who experienced a decrease in pain rating of 2 points on a 0- to 10-point numerical rating scale (NRS) from beginning pain to end pain, consistent with previous investigations.[2,11] A "sustained responder" was defined as an immediate responder who maintained at least a 2-point decrease at the first 2 postdischarge office visits in the Jefferson Headache Center, each of which was analyzed independently. These 2 visits are intended to occur at 30 and 90 days after discharge but because of scheduling reasons can vary by several weeks.

Continuous parametric data were analyzed using the Student *t* test for independent groups and the χ^2 test or Fisher exact test, as appropriate, for categorical data. All statistical analyses were performed using SYSTAT version 13 (Systat Software Inc, San Jose, California), with $P < 0.05$ set for statistical significance. Data are reported as mean ± SEM unless otherwise stated. For office visits 1 and 2, percentages of patients with sustained response were

TABLE 2. Additional Medications Used for Patients With Refractory Headache

	Immediate Responders (n = 48)	Nonresponders (n = 13)
IV/nasal DHE	14 (29.1%)	1 (7.7%)
IV NSAIDs	22 (45.8%)	6 (4.6%)
PO NSAIDs	8 (16.6%)	1 (7.7%)
IV neuroleptics	10 (20.8%)	1 (7.7%)
PO neuroleptics	24 (50%)	8 (61.5%)
IV anticonvulsants	2 (4.2%)	0
PO anticonvulsants	21 (43.8%)	5 (38.4%)

DHE indicates dihydroergotamine; NSAID, nonsteroidal anti-inflammatory drug; PO, by mouth.

TABLE 3. Adverse Events From Ketamine Infusions

Adverse Events	Immediate Responders (n = 48)	Nonresponders (n = 13)	*P*
Nystagmus	36 (75)	7 (54)	0.141
Sedation	23 (48)	8 (62)	0.319
Nausea/vomiting	19 (40)	4 (31)	0.564
Blurry vision	17 (35)	6 (46)	0.482
Hallucinations	13 (27)	4 (31)	0.794
Vivid dreams	5 (10)	3 (23)	0.234

Data are presented as n (%).

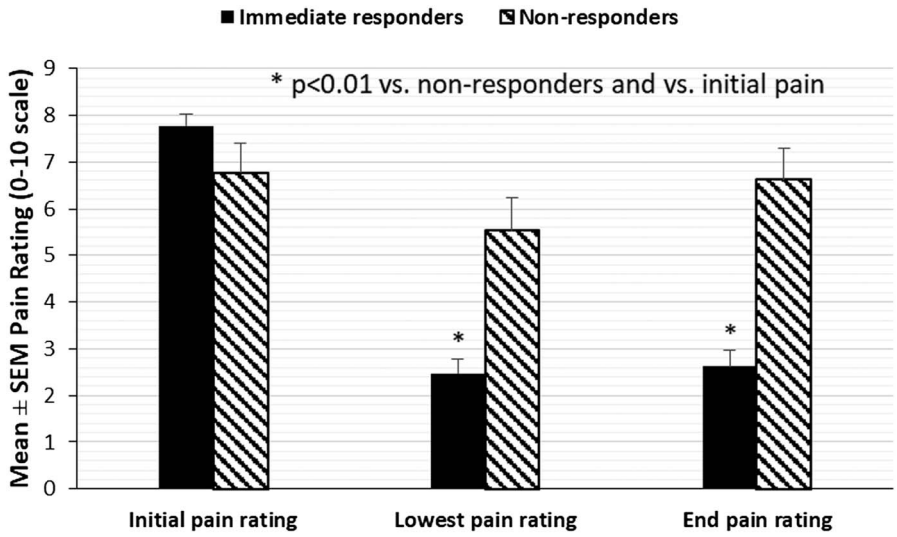

FIGURE 1. Pain experienced during admission by patients with refractory headaches being treated with continuous 5-day ketamine infusions.

based on patients with available data. Missing patients were not included in those analyses.

RESULTS

Headache Pain Outcomes

A total of 61 unique patients were identified and included in the study. Demographics are shown in Table 1. It is notable that 13 patients (27%) of the immediate responders and 5 patients (39%) of the nonresponders used daily opioids and met the criteria for MOH.[12] There was no difference between groups regarding MOH ($P = 0.499$). Additional medications administered during admission included dihydroergotamine, nonsteroidal anti-inflammatory drugs, neuroleptics, and anticonvulsants (Table 2). Fifty-nine of the 61 patients had a diagnosis of refractory migraine on admission, and 2 patients had cluster headache. The mean length of infusion was 5.1 ± 0.1 days. The mean pain rating on admission was 7.5 ± 0.2 out of 10 (NRS); this decreased to 3.4 ± 0.3 at the end of ketamine therapy ($P < 0.001$).

Using the predetermined definition of immediate responder as a patient with a decrease in pain rating of 2 out of 10 or greater, 48 (77%) of 61 patients were classified as immediate responders. There were no differences between immediate responders and nonresponders with regard to age, sex, history of opioid use, history of fibromyalgia, and presence of AEs (Tables 1 and 3). The mean NRS initial pain rating for immediate responders was 7.8 ± 0.23 and 6.8 ± 0.64 for nonresponders. At the end of treatment, the mean pain rating for immediate responders was 2.63 ± 0.28 compared with 6.62 ± 0.68 for nonresponders ($P < 0.01$; Fig. 1). The mean time to lowest pain rating was 4.56 days into the admission for immediate responders.

At the first office visit, which occurred 38.1 ± 4.7 days after hospital discharge, 52 of the original 61 patients had follow-up data available for analysis. Of the 52 patients, 21 (40%) had a sustained decrease in pain of 2 points and were classified as sustained responders. Thirty patients (58%) no longer had sustained response, and 1 patient was not an immediate responder but did improve at 1 month compared with the end of hospitalization. Sustained responders did not differ significantly from nonresponders with regard to age ($P = 0.437$) or sex ($P = 0.150$). At the

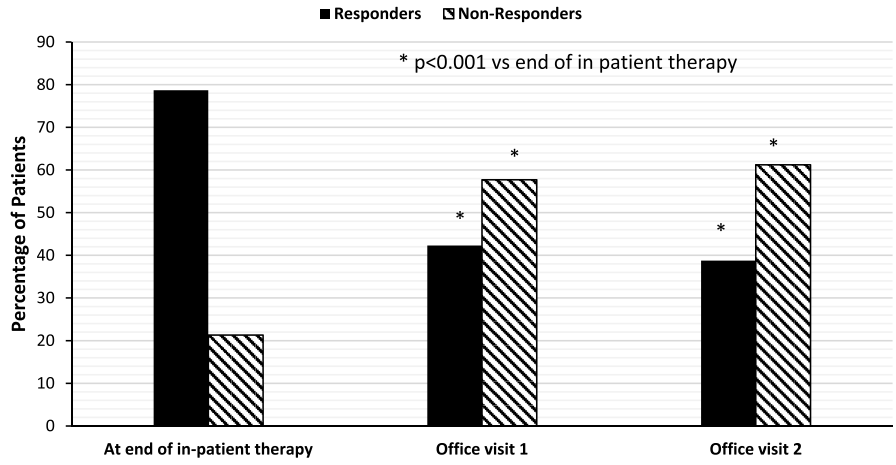

FIGURE 2. Percentage of patients characterized as responders acutely and at office visits 1 and 2.

TABLE 4. Ketamine Infusion Data

	Immediate Responders (n = 48)	Nonresponders (n = 13)	*P*
Mean starting rate, mg/h	11.0 (0.7)	10.8 (0.8)	0.853
Mean infusion rate, mg/h	43.7 (4.2)	44.1 (1.9)	0.933
Maximum infusion rate, mg/h	64.8 (3.0)	66.8 (7.2)	0.794

Data are presented as mean (SEM).

second office visit, which occurred 101.3 ± 8.8 days after hospital discharge, 49 of the original 61 patients had follow-up data available for analysis. Of these, 19 (39%) were classified as sustained responders (Fig. 2), whereas 30 (61%) were not sustained responders at the second office visit. There were no differences between sustained responders and nonresponders at this second office visit according to age ($P = 0.188$) or sex ($P = 0.979$).

Ketamine Infusion Characteristics

The mean starting ketamine infusion rate for all patients was 11.0 ± 0.6 mg/h (Table 4, Fig. 3). The mean weight was 85.4 ± 2.7 kg. The mean maximum ketamine infusion rate was 65.2 ± 2.8 mg/h, which is 0.76 mg/kg per hour. At the time of the lowest pain rating, the mean ketamine infusion rate was 54.5 ± 3.5 mg/h. There was no difference in mean ketamine infusion rate in immediate responders compared with nonresponders over the entire course of treatment (43.7 ± 4.2 vs 44.1 ± 1.9 mg/h; $P = 0.933$). There was also no difference in the mean maximum ketamine infusion rate between immediate responders and nonresponders (64.8 ± 3.0 vs 66.8 ± 7.2 mg/h; $P = 0.794$).

Adverse Events

Patients were asked daily about the presence of AEs, including central nervous system events (hallucinations, vivid dreams, blurry vision) and nausea and/or vomiting. Sedation was recorded based on nursing or physician observations. Results were recorded as "present" or "absent," and no severity was recorded. Results are shown in Table 3 in decreasing order of frequency. All AEs were considered mild and improved following a decrease in ketamine infusion rate, with the exception of 1 patient, a 52-year-old woman who experienced nausea, blurry vision, and sedation on day 2 of treatment and elected to stop ketamine.

DISCUSSION

Our retrospective study of inpatient ketamine infusion shows that more than three quarters of patients with refractory headache were immediate responders, and approximately half maintained the improvement up to 3 months after the infusion. Although it cannot be proven that ketamine was solely responsible for the pain relief because of the retrospective nature of the study, it is encouraging and suggests the need for larger, prospective studies in this challenging patient population. The US burden of chronic migraine, which comprised 97% of the diagnoses in our cohort, is substantial, with a prevalence of approximately 1% of the population.[13] The subset of this group carrying a refractory migraine diagnosis is approximately 5%,[13] and these patients have substantial disability and poor overall quality of life.

Our results mirror and expand upon other retrospective studies with positive results using ketamine for immediate relief of refractory headache.[2,3] One prospective, randomized, double-blind study reported that subcutaneous ketamine improved acute and subacute pain associated with migraine headaches in 17 patients, although the dosing strategy was unusual.[14]

Our patients achieved maximum pain relief after more than 4 days into their admission. This suggests that satisfactory pain relief may not be achieved after 1 day of treatment, and importantly, not achieving the desired effect during the first few days does not mean further improvement will not occur. Although the mean ketamine infusion rate increased from day 1 to day 4, by day 3 the mean ketamine rate was greater than 80% of the eventual maximum rate, yet patients continued to experience additional improvement in headache pain. Nonresponders experienced mild improvement by day 2 but no further reduction in headache intensity beyond that. Taken together, this suggests clinicians should be patient and wait at least 4 or 5 days before determining that someone did not respond to ketamine. For most patients, this requires a full 5-day treatment course.

What patient characteristics might help predict response? None of the demographic factors or the presence of fibromyalgia or current opioid use was significantly associated with response to ketamine. Fibromyalgia and opioid use are potential confounders,

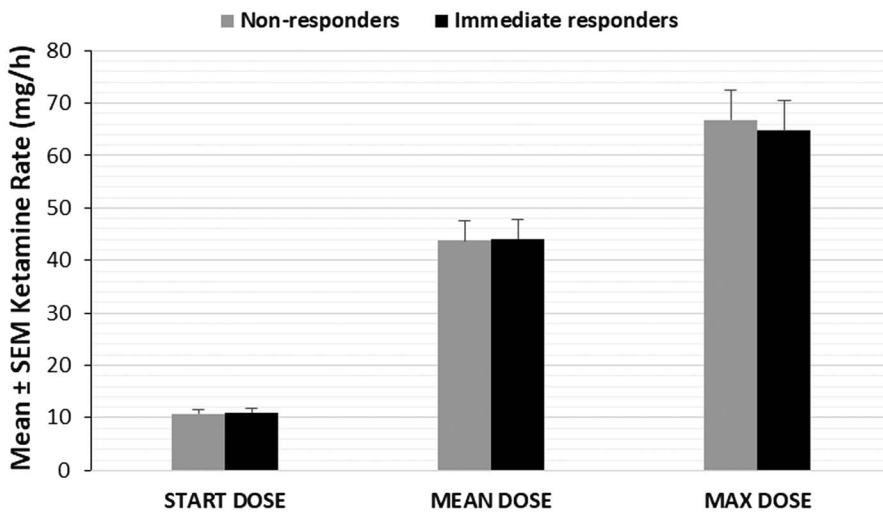

FIGURE 3. Ketamine infusion rates at various points of treatment.

given the evidence supporting ketamine for short-term relief in fibromyalgia,[15] as well as studies showing opioid-tolerant patients especially benefit from ketamine.[16,17] Well-designed prospective studies are needed to better elucidate these characteristics as retrospective data have limitations. Other factors might help predict response to ketamine, such as individual metabolism of the drug.[18] Metabolites of ketamine, including hydroxyketamine, dehydronorketamine, and other hydroxynorketamine molecules, may play a role in the treatment of depression,[19] and they could also be important in chronic pain conditions such as complex regional pain syndrome.[18] There is a subset of migraine and complex regional pain syndrome patients who have favorable response to ketamine, whereas others have minimal relief. Tailoring treatment based on likelihood of response would be useful to patients and clinicians. This is an area worthy of future study.

The widespread use of ketamine for refractory headache disorders remains challenging. The psychomimetic AEs, including hallucinations, vivid dreams, and other central nervous system excitation, associated with ketamine deter many from using it. In addition, because it is approved as an anesthetic, it requires monitoring that varies by state and hospital. The incidence of such undesirable AEs in a review of postoperative patients was approximately 7%.[20] In a mixed medical-surgical population receiving subanesthetic ketamine infusions, an incidence of 16% was reported, whereas in a refractory headache population this was as high as 20% of patients with a mean ketamine rate of 0.53 mg/kg per hour.[2] Our incidence of hallucinations (28%) was higher than these reported results, and this may have been a result of our fairly aggressive titration of ketamine with a mean maximum rate of 65 mg/h (0.76 mg/kg per hour). Despite our higher rates, only 1 patient discontinued infusion because of intolerance of AEs. This is encouraging as higher doses appear to be well tolerated by most patients.

In addition to the inherent limitations of any retrospective study, this study has several additional limitations. First, patients were not necessarily admitted for treatment during an acute exacerbation of migraine; thus, initial pain ratings may not have reflected the overall state of the headache disorder. Second, our ketamine protocol does not mandate a specific starting dose and allows for some clinical judgment in rate increases and decreases. There is variation in the titration strategy among our individual APMS physicians. Third, because 97% of patients in the study had a migraine diagnosis, it is not clear how generalizable these results would be to patients with other headache diagnoses. Last, we were unable to retrospectively determine with certainty if patients had any changes in treatment or other interventions after hospital discharge that could have affected level of pain at subsequent office visits. This limitation likely did not play a major role in the results as all patients in the study had refractory headaches and were unlikely to have responded to other minor interventions during that time.

In conclusion, subanesthetic ketamine infusion was associated with improved acute pain in a group of patients with refractory headaches, many of whom continued to experience decreased pain 3 months after treatment. Ketamine is a promising potential therapy for thousands of refractory patients who have not found relief elsewhere. Ketamine infusion is well tolerated within the context of our protocol. Prospective studies should focus on responder characteristics and optimal dosing strategies that minimize AEs while providing optimal headache relief.

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