Real-world study of intranasal ketamine for use in patients with refractory chronic migraine: a retrospective analysis

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ABSTRACT

Introduction Subanesthetic ketamine infusion has been used for managing refractory headache in inpatient or outpatient infusion settings. Intranasal ketamine may be an alternative option for outpatient care.

Methods A retrospective study was conducted at a single tertiary headache center to assess the clinical effectiveness and tolerability of intranasal ketamine in patients with refractory chronic migraine. Candidates who received intranasal ketamine between January 2019 and February 2020 were screened through an electronic medical record query. Manual chart reviews and structured telephone interviews were conducted on obtaining informed consent.

Results Of 242 subjects screened, 169 (79.9% women) of median (IQR) age 44 (22) years were interviewed. They reported a median (IQR) of 30 (9) monthly headache days and tried 4 (1) classes of preventive medications. Overall, they used 6 (6) sprays per day, with a median (IQR) of spray use of 10 (11) days per month. Intranasal ketamine was reported as 'very effective' in 49.1% and the quality of life was considered 'much better' in 35.5%. At the time of the interview, 65.1% remained current intranasal ketamine users and 74.0% reported at least one adverse event.

Conclusion In this descriptive study, intranasal ketamine served as an acute treatment for refractory chronic migraine by reducing headache intensity and improving quality of life with relatively tolerable adverse events. Most patients found intranasal ketamine effective and continued to use it despite these adverse events. Given the potential for overuse, it should be reserved for those clearly in need of more effective rescue treatment with appropriate safety precautions. Well-designed prospective placebo-controlled trials are necessary to demonstrate the efficacy and safety of intranasal ketamine in patients with migraine.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Intravenous ketamine, usually used for chronic pain and refractory headache, is limited to infusion settings. Intranasal ketamine, a more convenient alternative, has not been well studied for refractory headache.

WHAT THIS STUDY ADDS

⇒ This real-world study describes the usage pattern, effectiveness, and adverse event profiles of intranasal ketamine in patients with refractory chronic migraine.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our observational findings provide some evidence for the efficacy and safety of intranasal ketamine in the treatment of refractory headache. Our effect estimates can help inform sample size calculations for future randomized controlled trials.

INTRODUCTION

Refractory chronic migraine (rCM), defined as an inadequate response to multiple proven preventive and acute medications with a significant impact on disability and quality of life (QOL),[1] is highly pervasive in tertiary headache clinics. Ketamine, a dissociative anesthetic agent, has potential utility (off-label) for perioperative pain, chronic pain, depression, and headache,[2] especially when used with benzodiazepines to mitigate psychomimetic adverse events (AEs).[3] Ketamine, known as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, inhibits nitric oxide synthase, proinflammatory cytokine release, and serotonin reuptake. It antagonizes voltage-gated sodium channels, large conductance potassium channels, L-type voltage-dependent calcium channels, calcitonin gene-related peptide (CGRP) receptors, and nicotinic acetylcholine receptors. Ketamine also activates μ/δ opioid receptors, AMPA receptors, and $GABA_A$ receptors, and upregulates brain-derived neurotrophic factor.[2 4 5] There are two stereoisomers: S(+) and R(−), with the S(+) isomer 3–4 times more potent than R(−) but with quicker clearance. The active metabolite of ketamine, hydroxynorketamine, has a longer half-life than that of ketamine and lacks the addictive effect.[6 7] Hydroxynorketamine provides an additional mechanism of action; it blocks NMDA receptor currents with low affinity and weak voltage dependence and is effective when applied to resting receptors.[8] It also elicits antidepressant effects by inhibiting AMPA glutamate and α7 nicotinic cholinergic receptors.[4] With hydroxynorketamine's longer half-life, the frequent use of ketamine may lead to the accumulation of hydroxynorketamine to provide better pain inhibition, as seen in the ketamine infusion study.[9] The mechanism of action for ketamine

in antinociception is likely multifactorial beyond NMDA but remains unclear.[10]

To date, several randomized controlled trials (RCTs) have been published on subanesthetic ketamine infusion for headache management.[11] Since 2000, Thomas Jefferson University Hospital has been using subanesthetic ketamine infusions for multiple chronic pain conditions including chronic regional pain syndrome and headache. We have published several retrospective cohort studies demonstrating the potential utility of ketamine infusion in managing rCM.[9 12–14] However, intravenous (IV) ketamine typically requires dose titration and AE monitoring by a pain specialist in the hospital, thus limiting its use in the outpatient setting. Intranasal (IN) ketamine, with its simple storage and convenient administration, is an attractive alternative to IV administration. It has rapid systemic absorption without first-pass hepatic metabolism but with 25–50% bioavailability (higher than oral ketamine).[15] The FDA has recently approved esketamine (Spravato; Janssen, Raritan, New Jersey, USA), an IN S(+) enantiomer for treatment-resistant depression; its use in treating headache or migraine has not been studied.

Over the last few years, IN ketamine has been evaluated for acute pain management.[16 17] While there is some evidence behind IN ketamine as a treatment for headache disorders (eg, migraine, cluster headache, non-traumatic headache) in several studies,[18–23] its role in treating rCM has not been well described or validated. At our center, IN ketamine is often prescribed to patients with rCM who do not respond well to standard infusion treatments including dihydroergotamine and lidocaine, before or after a scheduled ketamine infusion. We hypothesized that IN ketamine alleviates acute headaches in patients with rCM as adjunctive therapy to their standard headache management. To better understand the real-world benefit of IN ketamine, we retrospectively reviewed the effectiveness and tolerability of IN ketamine in patients with rCM as outpatients at a tertiary headache center.

METHODS

This single-center study was approved by the Thomas Jefferson University Institutional Review Board (#20E.147). Our process involved retrospective chart reviews and telephone interviews with established patients at the Jefferson Headache Center (JHC). Patients who did not have success with multiple standard migraine treatments were offered IN ketamine scripts (100 mg/mL, 15–30 mL), which were formulated by a local compounding pharmacy to approximately 10 mg per 0.1 mL spray and instructed to use 1–2 sprays each nostril per dose every 15 min as needed with up to 20 sprays a day and 40 sprays a week at the discretion of their JHC providers. IN ketamine safety precautions were reviewed carefully with patients so the self-administered dosage could achieve sufficient benefit while avoiding addiction and misuse. All patients given IN ketamine scripts were required to sign a treatment contract agreeing to the recommended dosage, following up regularly, avoiding use before driving, refraining from drinking alcohol and using other controlled substances without our knowledge, and avoiding pregnancy. Although the usage frequency was kept flexible for the patient, its refill was restricted requiring regular clinical visits to evaluate adherence or any sign of misuse. Lack of effectiveness and contract violation would result in IN ketamine termination.

We identified patients who received IN ketamine scripts between January 1, 2019 and February 29, 2020 through an electronic medical record query. Eligible patients were at least 18 years of age at screening and received at least one electronic script for IN ketamine during the study period. All identified subjects were mailed a recruitment letter regarding the study, its goals, and the option to opt out. After a 60-day waiting period, identified patients were contacted by telephone to conduct structured interviews on obtaining verbal consent. Participants were excluded if they never filled the ketamine script, received IN ketamine for non-migraine diagnoses, or could not participate via telephone interview.

Two independent investigators performed chart reviews involving demographic information, headache diagnoses/characteristics, comorbidities, current and previous preventive/acute regimens, and the setting and reason for IN ketamine initiation. Each participant received a telephone interview to review multiple questions, including current IN ketamine regimen (dose, frequency), time to pain relief, consistency (how often/consistent does IN ketamine work) of pain relief and most bothersome symptoms, changes in pain level (11-point numerical rating scale) before and after use, global impression of effectiveness in treating headache (What was the overall impression of the spray's effectiveness in treating your headache: very effective, somewhat effective, no change, worse?), the overall impact on QOL while using IN ketamine (What was the overall impact on your life while using the spray: very effective, somewhat effective, no change, worse?), comparison with other rescue medications (Compared with the other abortive medications that you were taking for headache, how is the effectiveness of ketamine nasal spray in treating acute headaches: much better, somewhat better, no difference, somewhat inferior, much inferior?), and AEs. The collected information was stored on a HIPAA-compliant web-based REDCap electronic data capture tool hosted at Thomas Jefferson University.[24] On data cleaning and verification, the senior investigator determined final data approval.

Statistical analysis

De-identified data were analyzed using the statistical analysis program SPSS Statistics v.28 (IBM, Armonk, New York, USA). Categorical data were presented as percentages. Continuous variables were presented as arithmetic mean±SD or median (interquartile range) depending on the normality, which was determined using the Shapiro–Wilk test. Categorical variables were analyzed via χ^2 analysis or Fisher's exact test if expected counts were <5. Parametric or non-parametric tests for independent samples were used for continuous variables based on the normality. Missing data were considered at random and no imputation was performed. P values <0.05 were considered significant.

RESULTS

In total, 242 patients with rCM were prescribed IN ketamine during the study period and 169 were successfully contacted, consented, and interviewed. The remaining 55 patients could not be reached, and 18 declined participation. Table 1 shows the demographics, headache characteristics, preventive/acute medications, and comorbidities of the study population divided by the self-reported global impression of effectiveness (very effective vs others). While all patients had a migraine diagnosis, coexisting headache diagnoses included new daily persistent headache (n=22, 13.0%), post-traumatic headache (n=8, 17.8%), and idiopathic intracranial hypertension (n=5, 3.0%). The majority of patients reported daily headache (67.5%) and 84.6% tried more than three classes of preventive medications. They currently used a median of 2 (2) preventive medication

Table 1 Description of the study population

	Overall	Very effective	Not very effective	P value*
Sample size, n	169	83	86	
Demographics				
Caucasian, n (%)	161 (95.3)	79 (95.2)	82 (95.3)	0.96
Sex, n (%)				0.07
Male	34 (20.1)	19 (25.6)	15 (14.5)	
Female	135 (79.9)	64 (74.4)	71 (85.5)	
Median (IQR) age, years	43 (22)	42 (24)	45 (22)	0.39
Median (IQR) BMI, kg/m^2	29.6 (8.8)	29.6 (10.4)	29.1 (7.9)	0.26
Employment disability, n (%)	77 (45.6)	40 (48.2)	37 (43.0)	0.50
Headache characteristics				
Median (IQR) migraine years†	9 (13)	8 (9)	10 (15)	0.35
Median (IQR) monthly HA days	30 (9)	30 (2)	30 (10)	0.14
Daily HA, n (%)	111 (65.7)	60 (72.3)	54 (62.8)	0.19
Median (IQR) monthly bad HA days	15 (19)	15 (19)	15 (20)	0.94
Median (IQR) monthly disabling HA days	13 (17)	15 (16)	10 (19)	0.47
Aura, n (%)	65 (38.5)	32 (38.6)	33 (38.4)	0.98
Median (IQR) previous preventive classes	4 (1)	4 (1)	4 (2)	0.41
Median (IQR) current preventive classes	2 (2)	2 (2)	2 (2)	<0.01‡
CGRP mAb, n (%)	89 (52.7)	51 (61.4)	38 (44.2)	0.03‡
Antiepileptics, n (%)	78 (46.2)	43 (51.8)	35 (40.7)	0.15
OnabotA, n (%)	73 (43.2)	34 (41.0)	39 (45.3)	0.57
Antidepressant, n (%)	69 (40.8)	39 (47.0)	30 (34.9)	0.11
Antihypertensive, n (%)	45 (26.6)	29 (34.9)	16 (18.6)	0.02‡
Median (IQR) current acute med classes	2 (2)	2 (2)	1 (2)	0.03‡
Neuroleptics, n (%)	82 (48.5)	46 (55.4)	36 (41.9)	0.08
NSAIDs, n (%)	57 (33.7)	35 (42.2)	22 (25.6)	0.02‡
DHE, n (%)	52 (30.8)	29 (34.9)	23 (26.7)	0.25
Gepants/ditan, n (%)	38 (22.5)	18 (21.7)	20 (23.3)	0.81
Triptans, n (%)	34 (20.1)	17 (20.5)	17 (19.8)	0.91
Simple/combined analgesics, n (%)	31 (18.3)	13 (15.7)	18 (20.9)	0.38
Opioids, n (%)	21 (12.4)	9 (10.8)	12 (14.0)	0.54
Comorbidity				
Neck pain, n (%)	104 (61.5)	51 (61.4)	53 (61.6)	0.98
Anxiety, n (%)	99 (58.6)	52 (62.7)	47 (54.7)	0.29
Depression, n (%)	93 (55.0)	53 (63.9)	40 (46.5)	0.02‡
Insomnia, n (%)	74 (43.8)	35 (42.2)	39 (45.3)	0.68
Low back pain, n (%)	70 (41.4)	36 (43.4)	34 (39.5)	0.61
Mild concussion, n (%)	58 (34.3)	32 (38.6)	26 (30.2)	0.26
TMJ disorder, n (%)	39 (23.1)	17 (20.5)	22 (25.6)	0.43
Hypothyroidism, n (%)	26 (15.4)	14 (16.9)	12 (14.0)	0.60
PTSD, n (%)	25 (14.8)	15 (18.1)	10 (11.6)	0.24
OSA, n (%)	23 (13.6)	16 (19.3)	7 (8.1)	0.04‡
Bipolar, n (%)	16 (9.5)	12 (14.5)	4 (4.7)	0.03‡

*P values compare very effective versus not every effective groups using the χ^2 test or non-parametric t-test. All continuous data were non-normally distributed.
†Statistically significant.
‡22 and 28 cases missing in the very effective and not very effective groups, respectively.
BMI, body mass index; CGRP mAb, calcitonin gene-related peptide monoclonal antibody; DHE, dihydroergotamine; HA, headache; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; onabotA, onabotulinumtoxinA; OSA, obstructive sleep apnea; PTSD, post-traumatic stress disorder; TMJ, temporomandibular joint.

classes, where the most common current preventive medication was CGRP monoclonal antibody. A median of 2 (2) acute medication classes were used, with neuroleptics being the most common. Greater numbers of preventive and acute medication classes were prescribed in the very effective group. While neck pain was the most common comorbidity, more depression, obstructive sleep apnea, and bipolar disorder were found in the very effective group.

The most common reasons for initiating IN ketamine included incomplete response to prior acute medications (100, 59.2%), incomplete response to prior preventives (52, 30.8%), prior benefit from IV ketamine (38, 22.5%), and unsuccessful lidocaine infusion (22, 13.0%). Forty-one (24.7%) and 46 (27.7%) patients were offered IN ketamine before and after ketamine infusion, respectively; 47.6% had never received ketamine infusion. When evaluating overall effectiveness, 83 (49.1%) found

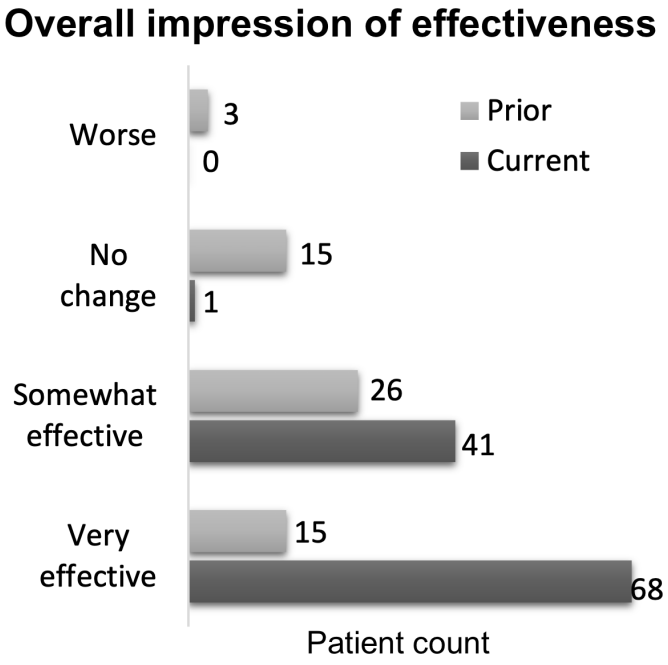

Figure 1 Overall impression of effectiveness comparison between current and prior intranasal ketamine users.

it very effective and 67 (39.6%) found it somewhat effective (figure 1). Within the same group, 60 (35.5%) and 72 (42.6%) found the overall impact of IN ketamine on their QOL to be much better and somewhat better, respectively (figure 2). Current IN ketamine users reported better responses overall. Compared with other acute headache medications, IN ketamine was much better (73, 43.2%), somewhat better (50, 29.6%), no difference (18, 10.7%), somewhat inferior (15, 8.9%), and much inferior (5, 3.0%).

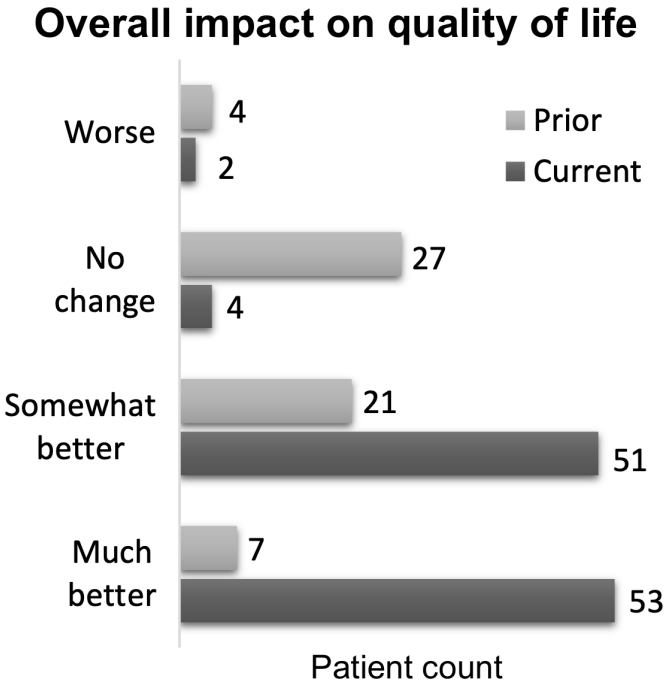

Figure 2 Overall impact on quality of life comparison between current and prior intranasal ketamine users.

Table 2 shows the usage patterns and effectiveness metrics of IN ketamine. Most patients were current IN ketamine users (n=110, 65.1%) at the time of the interview. Non-current users reported last IN ketamine use 7.5 (9) months ago. Thirty-seven (21.9%) reported using IN ketamine >15 days per month, 23 (13.6%) were daily users, and 31 (18.3%) used >10 sprays per day. There was no difference in per-day spray use between daily and non-daily users (6 (6) vs 6 (6), p=0.58). IN ketamine was used more frequently in the very effective group, but there was no total dose difference between them. Overall, there was a decrease in pain intensity with >70% treatment response consistency, particularly in those reported as very effective. Almost three-quarters reported less use of acute medication when using IN ketamine.

Table 3 lists the AEs reported by the participants. In all, 125 patients (74.0%) reported at least one AE. Fatigue and double vision/blurred vision were the most common, followed by cognitive AEs (eg, confusion/dissociation, vivid dreams, hallucination). In addition, among 142 participants with laboratory data, alanine and aspartate transaminase elevations (>3× upper normal limit) were found in 4.9% (n=7) and 2.1% (n=3), respectively, without bilirubin elevation. Short-term transaminase elevations were discovered during inpatient ketamine infusion (n=4), while others were due to medical issues (eg, fatty liver, gallstones). Ketamine nasal spray usage continued afterwards without complication.

DISCUSSION

In this retrospective single-center study with 169 interviewed participants, most had rCM with daily headache and comorbid anxiety/depression at the time of the interview. This population failed multiple preventive medication classes and often required various classes of acute medications but with inadequate control of their pain. While effective treatment options are limited, as-needed IN ketamine seemed to have mitigated acute headache pain intensity and reduced other acute medication use. Almost half of the participants considered IN ketamine to be very effective, and more than two-thirds of patients found it improved their QOL. Almost three-quarters reported having at least one AE, particularly fatigue, vision disturbances, and cognitive issues. There were a few cases of elevated liver function tests, but most were discovered during ketamine infusion. These AEs were usually short-lasting, and patients continued using IN ketamine with caution afterwards.

To date, there are only a limited number of studies using IN ketamine for headache treatment (online supplemental appendix 1). In 2000, Kaube *et al* presented a case series of 11 patients with familial hemiplegic migraine who self-administered 25 mg of IN ketamine. Five showed reduced severity and duration of the neurological deficit.[18] In 2013, Afridi *et al* reported the first double-blind RCT comparing IN ketamine 25 mg against IN midazolam 2 mg in 18 patients with migraine with prolonged aura in both inpatient and outpatient settings. IN ketamine reduced the severity (p=0.032) but not the duration of the aura, whereas midazolam had no effect.[19] In the THINK trial (single-blind RCT), Benish *et al* compared IN ketamine (0.75 mg/kg) versus IN ketamine (0.015 mg/kg) + IV metoclopramide (10 mg) + oral diphenhydramine (25 mg) in 53 patients with primary headache syndrome in the emergency department (ED). The average change in the pain visual analog scale at 30 min post-intervention (the primary endpoint) was 22.2 mm in the control arm versus 29.0 mm in the IN ketamine arm (effect size difference 6.8 mm (95% CI −5.8 to 19.4); no statistically significant

Table 2 Evaluation of intranasal ketamine effectiveness

	Overall	Very effective	Not very effective	P value*
Current intranasal ketamine user, n (%)	110 (65.1)	68 (81.9)	42 (48.8)	<0.001†
Median (IQR) number of spray use days per month‡	10 (11)	12 (11)	8 (10)	0.04†
Daily use, n (%)	23 (13.6)	13 (16.0)	10 (11.9)	0.44
Median (IQR) number of sprays per day	6 (6)	6 (6)	6 (6)	0.38
Median (IQR) total dose§	58 (96)	60 (123)	48 (82.5)	0.11
Median (IQR) pain intensity before spray‡	8 (2)	8 (1)	8 (2)	0.03†
Median pain intensity after spray (IQR)‡	5 (3)	4 (2)	6 (3)	<0.001†
Median pain intensity change (IQR)‡	3 (2)	3 (2)	2 (2)	<0.001†
Median pain relief onset (min)¶	27.5 (52)	18 (52)	30 (82)	0.13
Pain relief consistency (%)‡	80 (30)	88 (15)	70 (55)	<0.001†
MBS relief consistency (%)‡	75 (45)	80 (20)	50 (65)	<0.001†
Use less other acute med, n (%)	120 (71.0)	68 (81.9)	52 (60.5)	<0.01†

*P values compare very effective versus not very effective groups using the χ^2 test or non-parametric t-test. All continuous data were non-normally distributed.
†Statistically significant.
‡1–3 cases missing in the very effective and not very effective groups.
§Total dose was calculated by number of spray use days /month multiplied by number of sprays/day.
¶ 11 and 2 cases missing in the very effective and not very effective groups, respectively.
IQR, interquartile range; MBS, most bothersome symptom.

difference).[20] Recently, Sarvari *et al* investigated the efficacy of IN ketamine (0.75 mg/kg) versus IV ketorolac (30 mg) in a double-blind RCT in 140 patients with non-traumatic acute headache in the ED. Pain reduction was significantly greater with IN ketamine than with IV ketorolac at 30, 60, and 120 min.[23] These RCTs show that IN ketamine may be as effective as the standard IV headache regimen. Apart from RCTs, Turner *et al* retrospectively reviewed 34 patients with status migrainosus receiving IN ketamine (0.1–0.2 mg/kg) in an inpatient setting. Twenty-five (73.5%) were responders with an average pain score reduction of −7.2 from admission to discharge,[21] suggesting potential utility in severe migraine. Petersen *et al* also showed that IN ketamine 15 mg every 6 min (maximum five uses), under in-hospital observation, could reduce pain intensity by 1.1 (95% CI −0.6 to 2.7) in 15 min and 4.3 (95% CI 2.4 to 6.2) in 30 min among 20 patients with cluster headache.[22] Esketamine, a S-enantiomer of ketamine, was approved by the FDA for treatment-resistant depression. Considering that depression and anxiety are significant comorbidities associated with headache disorders, IN ketamine could potentially treat depression in patients with rCM. It is important to know that all studies reported AEs, including dizziness, nausea, increased blood pressure/heart rate, fatigue, and mood change. While these AEs were expected, they were temporary and resolved within a few hours. Based on these studies, IN ketamine appeared to reduce head pain quickly and effectively, at least for common headaches in the ED. Our study, which included mostly patients with rCM, further expands the potential utility of IN ketamine in patients with refractory headache.

Table 3 Reported adverse events by surveyed patients

Presence of ≥1 adverse events, n (%)	125 (74.0)
Fatigue, n (%)	37 (21.9)
Double/blurred vision, n (%)	36 (21.3)
Confusion/dissociation, n (%)	34 (20.7)
Nausea, n (%)	28 (16.6)
Dizziness, n (%)	23 (13.6)
Nasal discomfort/epistaxis, n (%)	21 (12.4)
Vivid dreams, n (%)	17 (10.1)
Hallucination, n (%)	13 (7.7)
Ageusia, n (%)	10 (5.9)
Increased anxiety, n (%)	6 (3.6)
Vomiting, n (%)	5 (3.0)
Tremor, n (%)	5 (3.0)
Imbalance, n (%)	5 (3.0)
Worsened/rebound headache, n (%)	4 (2.4)

The optimal dosage for IN ketamine that is safe and effective remains to be determined. At the time of writing, IN ketamine use for headache or pain remains off-label, and guidelines on the optimal dose of IN ketamine are lacking. IN ketamine has a Tmax of 20–40 min (norketamine even longer) and a wide bioavailability of 8–45%. However, such metrics were gathered from blood and may not reflect the actual distribution of ketamine in the trigeminal system. In our study, median pain relief onset was 27.5 (52) min, but varied greatly. This variation in onset may reflect the effect of ketamine (and its metabolites) and its pharmacokinetic property. It is important to understand that IN absorption varies by the nasal spray apparatus, nasal passage, site of deposition, spray viscosity, and other factors. In our study, ketamine was delivered via a traditional metered-dose spray pump with 100 µL (10 mg) per spray (without any mucoadhesive or permeabilization agent), generating particles 50–100 µm in diameter. Some studies used MAD Nasal™, which is an atomization device that produces smaller particles (30–100 µm) and delivers deeper/higher into the nasal cavity and less to the lung than the typical nasal spray.[25] Compared with the lower nasal space, its upper counterpart allows for more efficient absorption due to differences in olfactory epithelium, lower mucociliary clearance, and richer vascular/lymphatic system.[26] Lipophilic small molecules such as ketamine can be transported via transcellular, paracellular, and perineural pathways via trigeminal nerves,[26 27] offering a possible delivery route to the trigeminal ganglia bypassing the first-pass metabolism and blood–ganglion barrier. Even though our participants used an average of 60–80 mg/day, which is much lower than the infusion daily dose (0.5–1 mg/kg/hour; 960–1920 mg daily for an 80 kg person), the cephalic analgesic effect and psychometric AEs were still apparent. Intermittent use of IN ketamine does not

produce stable steady-state plasma levels but a series of peaks and troughs, thus generating more peak level AEs. In addition, it is plausible that the local concentration within the trigeminal system may be higher than the plasma concentration, creating a localized antinociceptive effect with lower systemic AEs.

Since IN ketamine has a relatively short half-life (<2 hours),[28] patients with refractory headache may tend to use it more regularly. At this time, without a specific biomarker reflecting the local concentration of ketamine, the optimal dosage may require individual titration to find a good balance between safety and efficacy. Of note, the transportation of molecules through the nasal cavity is limited by small volume (100–200 µL), limited surface area, short retention time, low mucosal permeability, and high individual variability.[29] Excessive sprays in the nasal cavity may enter the stomach and are not effectively absorbed, thus limiting the potential for significant overdosing in a single use.[30] This may explain why most patients (81.7%) used no more than 10 sprays per day to avoid wasting, and why serious AEs were not observed in this study. Still, dependence behavior can develop (eg, 23 (13.9%) used it daily and 37 (21.9%) used it ≥15 days/month) and should be addressed carefully and individually, as some may respond only to repeated IN ketamine while some may overuse it. It is worth noting that ketamine infusion is usually used to facilitate the withdrawal of analgesics in medication overuse headache. Whether overusing IN ketamine leads to rebound headaches is yet to be determined.

Clinicians should only consider the use of a potentially addictive medication such as ketamine for significantly disabled patients with migraine. The use of opioids for migraine has dramatically decreased due to serious AEs, changes in treatment guidelines, and lack of efficacy with long-term use despite appropriate monitoring. At Jefferson, we have more than 20 years of experience in ketamine infusion for chronic pain and headache and have written guidelines on ketamine use.[2] Understanding the potential risk for outpatient IN ketamine use, we have established several strategies/safeguards to ensure patient safety. Providers are required to go over the treatment agreement point by point with the patients, explaining the risks and rules of use. All prospective IN ketamine users are required to sign the treatment agreement and monitor/report any short-term AEs (eg, sedation, dissociation, anxiety) and long-term AEs (eg, hypertension, cognitive/mood change, liver/bladder dysfunction). We routinely ask patients to titrate from a lower dose (one or two sprays; start low, titrate slow) and limit the IN ketamine use for their headache (not other somatic pain) to a maximum of 20 sprays a day (maximal 40 sprays a week) with no more than 1–2 refills (15–30 mL per month with no early refills). After that, a clinical visit is required to assess IN ketamine response, AEs, and any sign of misuse such as dose escalation or requests for early refills. Re-education on ketamine safety is offered by the clinical team and at the compounding pharmacy. Since some ketamine-related AEs could lead to higher levels of care (eg, emergency room, hospitalization), patients are instructed to cautiously try different dosages while monitoring potential AEs of ketamine to avoid overuse or intoxication. Prolonged frequent use of IN ketamine is strongly discouraged to avoid long-term sequelae (eg, ulcerative cystitis, cognitive and mental health issues).

Strengths and weaknesses

Our retrospective study described the effectiveness and tolerability of IN ketamine as an acute outpatient treatment for rCM in adults. The reason for discontinuation was not evaluated. The data were collected through chart review and structured interviews, offering cleaner and more detailed information than chart review alone. However, this study was based on a single tertiary headache center, with the study population being primarily young Caucasian women. Consequently, the study results may have limited generalizability. In manual chart reviews, data are often limited by clinical notes, which may not be as accurate and comprehensive for research use. Although we supplemented it with structured telephone interviews, not everyone responded (30% were not interviewed in our study) and the collected information likely suffers from selection bias (eg, more positive IN ketamine responders participated) and recall biases (eg, only positive responses remembered and reported). In addition, the questionnaires on effectiveness and QOL impact were biased toward positive rather than negative outcomes, thus affecting the validity of patient-reported outcomes. Non-anonymity can also lead to self-reporting bias. Since this study is not a double-blind placebo-controlled trial, the level of evidence is limited regarding clinical management recommendations. Most participants used IN ketamine concomitantly with other abortive and preventive medications. Therefore, it is challenging to assess the therapeutic benefit of IN ketamine in isolation. Regarding the safety profile of IN ketamine, many AEs overlapped with migraine-associated symptoms, including but not limited to nausea and blurry vision. Whether these AEs led to higher levels of care was not studied but, in our clinical experience, serious AEs from IN ketamine were rarely seen. However, the actual safety profile should be further evaluated in a placebo-controlled trial.

CONCLUSION

This retrospective study suggests that IN ketamine may offer a pain-relieving effect with limited morbidity for rCM in the outpatient setting. The optimal IN ketamine dosage, however, remains to be explored. Our data should help to inform sample size calculations for the needed placebo-controlled trials involving IN ketamine for acute treatment of migraine.

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Patient consent for publication Not applicable.

Ethics approval The study was reviewed by the Thomas Jefferson University IRB (Control #20E.147) and determined to be exempt from full IRB review. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The deidentified data may be available upon reasonable request.

of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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