Intranasal ketamine for abortive migraine therapy in pediatric patients: a case series

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BACKGROUND

Migraine is a common presentation in adolescents and children in emergency departments (EDs) and inpatient visits. It is often treated with nonsteroidal anti-inflammatory drugs, dopamine receptor antagonists, triptans, or dihydroergotamine (DHE). Some cases, however, are refractory to traditional medications and options become narrowed.[1,2] Restricting therapy further, DHE is currently on indefinite shortage.[3] Ketamine, a lipophilic, rapid-acting, N-methyl-D-aspartate (NMDA) antagonist, has emerged as a promising therapeutic option.[4,5] Excitatory glutamate signaling may be inhibited by ketamine via NMDA antagonism. This action could suppress cortical spreading depression (CSD) and alleviate migraines with and without aura.[5]

Reports in mixed migraine patient populations described statistically significant pain score reductions (7.1 to 3.8; p<0.0001) with intermittent intravenous ketamine[6] and diminished severity with ketamine infusions (0.12-0.42 mg/kg/hour)[7] without serious adverse effects (AEs).[6,7] Intranasal (IN) ketamine 25 mg in migraine patients with prolonged aura demonstrated statistically significant reduced aura severity (p=0.032).[4] Reports of efficacy and safety with IN ketamine (0.3-0.5 mg/kg/dose) in pediatric patients with various pain diagnoses have been published[8-13], but pediatric migraine data with IN ketamine is lacking.

OBJECTIVE

Report efficacy and safety of IN ketamine in pediatric patients with refractory migraine.

METHODS

Inclusion
- Pediatric patient (≤ 18 years old)
- Presenting to CCMC ED or inpatient
- Pain or Neurology Services deem patient refractory

Administration
- Intranasal ketamine
- 0.1-0.2 mg/kg/dose (maximum 25 mg/dose)
- Administered every 15 minutes (maximum of 5 doses)

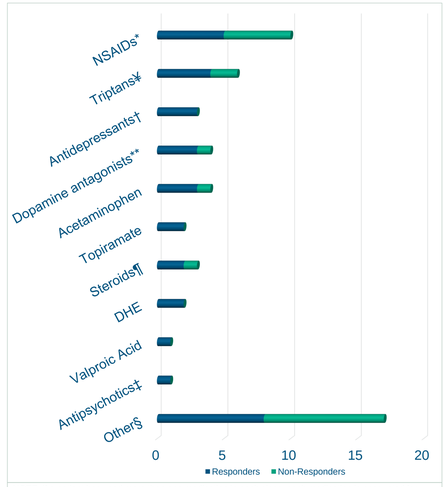
Monitoring
- Numeric pain scores[14]
- Vitals[15,16] during and 1 hour post administration
- Patient reported side effects (if stated)
- Inpatient admissions and readmissions ≤ 72 hours

DEMOGRAPHICS

Patient Characteristic	Total n (%)*
Encounters Reviewed – *n*	
Visits	11
Patients	9
Sex – *female*	8 (88.9)
Age – *years, mean (range)*	15.36 (12 – 17)
Weight – *kg, mean (range)*	68.9 (38.4 – 128.2)
Location of Ketamine Initial Dose	
ED	7 (63.6)
Inpatient	4 (36.4)
Migraine duration at presentation – *days, mean (range)*	
Responders	44.57 (5 – 81)
Non-Responders	5 (1 – 9)
Response Classification	
Responders	7 (63.64)
Non-Responders	4 (36.36)
Comorbid diagnoses at presentation, *n=9*	
Anxiety disorder	2 (22.2)
Brain structure abnormality (i.e. pseudotumor cerebri/benign intracranial hypertension, tumor)	3 (33.3)
Conversion disorder	1 (11.1)
Depression	2 (22.2)
History of brain injury	3 (33.3)
Post Traumatic Stress Disorder	1 (11.1)
Other (i.e. ADHD, antisocial personality disorder, myalgia, panic disorder, trigeminal neuralgia)	7 (77.8)

*unless otherwise denoted

Previously Trialed Medications Prior to Admission



NOTE: if a patient has used more than one medication in each class, each medication is accounted for

** ibuprofen, ketorolac, naproxen*
¥ naratriptan, rizatriptan, sumatriptan
† amitriptyline, nortriptyline
*** metoclopramide, prochlorperazine, promethazine*
¶ methylprednisolone, prednisone, prednisolone
‡ olanzapine
§ acetaminophen/butalbital/caffeine, bupivacaine/lidocaine, diphenhydramine, cyproheptadine, opioids/opioid combinations, onabotulinumtoxin, ondansetron, propofol, tramadol, trazodone

RESULTS

Dosing and Patient Response

	Responders (n=7) Mean (range)*	Non-Responders (n=4) Mean (range)*	Total (n=11) Mean (range)*
Dosing			
Weight based – *mg/kg/dose*	0.14 (0.078-0.195)	0.167 (0.14-0.195)	0.15 (0.078-0.195)
Actual – *mg/dose*	10 (10-10)	8.88 (6.76-10)	9.59 (6.76-10)
Total # doses administered	4.14 (2-5)	4 (2-5)	4.09 (2-5)
Pain Reduction			
From Admission to Treatment Completion	**-6.86** (-9 to -5)	**-0.5** (-2 to 2)	**-4.55** (-9 to 2)
From Admission to Discharge	-7.43 (-10 to -2)	-7.25 (-10 to -5)	-7.36 (-10 to -2)
Inpatient Admission – *if initiated in ED, n/N (%)*	0/3 (0)	4/4 (100)	4/7 (57.14)
Length of Stay – *days*	**2.43** (0-7)	**4.75** (3-8)	**3.27** (0-8)
Readmissions – *≥ 72 hours*	0	0	0

*unless otherwise denoted

Pain Score Response to IN Ketamine

RESULTS (continued)

Adverse Reactions

Reaction	Responders (n=7) n (%)	Non-Responders (n=4) n (%)	Total (n=11) n (%)
Total	6 (85.71)	4 (100)	10 (90.91)
Hypertension (mild)	5 (71.43)	3 (75)	8 (72.73)
Tachypnea (mild)	5 (71.43)	4 (100)	9 (81.82)
Tachycardia (mild)	3 (42.86)	1 (25)	4 (36.36)
Dizziness	2 (28.57)	0	2 (18.18)
Dysphoria	1 (14.29)	0	1 (9.09)
Flushing	1 (14.29)	0	1 (9.09)

Comorbid Diagnoses by Patient Response to IN Ketamine

Diagnoses	Responders (n=5) n (%)	Non-Responders (n=4) n (%)
Anxiety disorder	1 (20)	1 (25)
Brain structure abnormality (i.e. pseudotumor cerebri/benign intracranial hypertension, tumor)	0	3 (75)
Conversion disorder	1 (20)	0
Depression	1 (20)	1 (25)
History of brain injury	2 (40)	1 (25)
Post Traumatic Stress Disorder	1 (20)	0
Other (i.e. ADHD, antisocial personality disorder, myalgia, panic disorder, trigeminal neuralgia)	4 (80)	3 (75)

STRENGTHS AND LIMITATIONS

STRENGTHS
- First report utilizing IN ketamine in pediatric patients for migraine
- Easy and safe administration and monitoring

LIMITATIONS
- Retrospective in nature
- Small sample
- No set study protocol to precisely analyze a specific regimen
- Difficult to discern if some adverse reactions (i.e. vital signs) are due to pain or medication

CONCLUSIONS

Intranasal ketamine appears to be safe and effective for pediatric migraine treatment, particularly in patients with prolonged migraine. Patients with significant comorbidities did not respond as well and it is likely that patients who had an identifiable cause for their headache did not have true migraine. Our experience supports efficacy with lower IN ketamine doses (0.1–0.2 mg/kg/dose in repeated doses) in abortive migraine therapy with minimal AEs. Larger trials are warranted to substantiate ketamine's efficacy, optimal dose, and safety for abortive migraine therapy in pediatric patients.

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