Comparison of Intranasal Ketamine, Dihydroergotamine, and Valproic Acid for Abortive Migraine Treatment in a Pediatric Emergency Department

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BACKGROUND

Pediatric migraineurs in emergency departments (EDs) are often treated with nonsteroidal anti-inflammatory drugs (NSAIDs), dopamine receptor antagonists (DRAs), or dihydroergotamine (DHE).[1,2] Intravenous (IV) DHE has become a standard abortive migraine treatment[3], but DHE is contraindicated in some instances[4], and an alternative such as IV valproic acid (VPA) is utilized.[1,2] Unfortunately, VPA's efficacy is variable, and is often cited to be less efficacious than metoclopramide or ketorolac for pediatric migraine.[5]

Fortuitously, intranasal ketamine (INK) has emerged as a potentially efficacious option for migraine with or without aura. Reports of efficacy and safety with IN ketamine in pediatric patients with various pain diagnoses have been published.[6-12] In a recent quality assurance review at our institution, 25/34 pediatric migraineurs (73.5%) responded to INK 0.1-0.2 mg/kg/dose (mean pain reduction: -7.2). All AEs were mild and transient. Despite promising – albeit, minimal – data, INK's place in therapy is yet to be determined.

OBJECTIVE

The aim of this study is to compare efficacy and safety of INK to DHE and VPA in pediatric ED patients to better elucidate INK's place in therapy.

METHODS

Single-center, retrospective review of patients presenting to Cook Children's Medical Center ED with chief complaint of migraine for treatment with INK, DHE, or VPA

Inclusion Criteria
- Age 0 to 18 years
- First administration of INK (December 2016 - September 2017)
- First administration of DHE or VPA (March 2018 - February 2019)
- Treatment initiated in the ED

Exclusion Criteria
- Headache etiology determined not to be a migraine upon review by a neurologist
- Repeat administrations of INK, DHE, or VPA

Data Collection/Endpoints

Demographics
- Age; race/ethnicity; sex; weight
- Relevant comorbid conditions
- Migraine duration prior to treatment
- Migraine classification
- Medications given on admission prior to primary treatment

Efficacy
- Admission pain scores[13]
- Pain scores immediately after primary treatment and at discharge[13]
- ED to inpatient admissions
- Length of stay
- Readmissions ≤72 hours

Safety
- Vital signs (during and up to 1 hour after treatment)[14,15]
- Patient reported side effects
- Clinician reported side effects

Statistical Analysis

Data were analyzed via IBM SPSS software utilizing indepedent t-test or chi-square with a confidence interval of 95% and p-value <0.05.
Data between INK vs DHE and INK vs VPA were analyzed separately.

DEMOGRAPHICS

Patient population	INK *n=22*	DHE *n=16*	p-value	VPA *n=13*	p-value
Age† *(years)*	14.5 ± 2.7	14.4 ± 1.3	NS	14.7 ± 1.7	NS
Sex					
Male	2	5	NS	4	NS
Female	20	11		9	
Race/ethnicity					
Caucasian/Non-Hispanic	18	9	NS	10	NS
Caucasian/Hispanic	2	3		1	
African American	2	4		2	
Weight† *(kg)*	62.2 ± 20.3	56.9 ± 7.6	NS	67.5 ± 19.7	NS

NS, not significant; Reported as n (%) unless otherwise noted
† mean ± SD

DEMOGRAPHICS

Migraine Characteristics	INK	DHE	p-value	VPA	p-value
Duration of migraine at presentation† *(days)*	19 ± 27.5	14 ± 18	NS	4.4 ± 5.2	NS
Status migrainosus	10 (45.5)	9 (56.3)	NS	6 (46.2)	NS
Migraine classification					
Chronic	12 (54.5)	10 (62.5)	NS	7 (53.8)	NS
Episodic	10 (45.5)	6 (37.5)		6 (46.2)	
Migraine with aura	5 (22.7)	2 (12.5)	NS	1 (7.7)	NS

NS, not significant; Reported as n (%) unless otherwise noted
† mean ± SD

Inpatient Medications Prior to Primary Treatment	INK	DHE	p-value	VPA	p-value
Acetaminophen	1 (4.5)	0 (0)	NS	0 (0)	NS
Diphenhydramine	16 (72.7)	8 (50)	NS	9 (69.2)	NS
DRAs	11 (50)	15 (93.8)	**<0.001**	12 (92.3)	**<0.001**
Fluids/hydration	17 (77.3)	14 (87.5)	NS	13 (100)	**0.021**
Magnesium sulfate	0 (0)	6 (37.5)	**0.009**	4 (30.8)	**0.04**
NSAIDs	15 (68.2)	12 (75)	NS	9 (69.2)	NS
Ondansetron	9 (40.9)	8 (50)	NS	5 (38.5)	NS

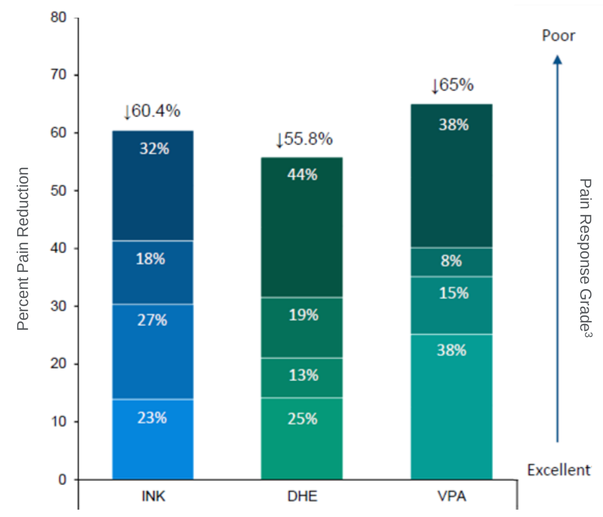
NS, not significant; Reported as n (%)

RESULTS

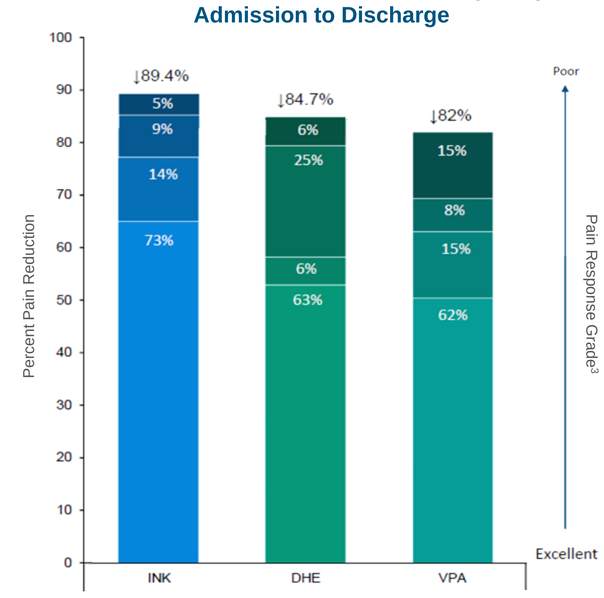
Outcomes	INK	DHE	p-value	VPA	p-value
Responder	18 (81.8)	8 (50)	NS	8 (61.5)	NS
Cumulative Dose† *(mg)*	29.659 (0.454)	0.294 (0.005)	--	789.23 (13.64)	--
Length of stay‡ *(days)*	0.4 ± 0.5	0.2 ± 0.4	NS	0.6 ± 0.5	NS
ED to inpatient admission	6 (27.3)	11 (68.8)	**0.01**	4 (30.8)	NS
Readmission ≤72 hours	3/16 (18.8)	1/5 (20)	NS	3/9 (33.3)	NS

NS, not significant; Reported as n (%) unless otherwise noted
† mean (mean/kg); ‡ mean ± SD

Mean Percent Pain Score Reduction Stratified by Response Scale: Admission to Primary Treatment Completion



Mean Percent Pain Score Reduction Stratified by Response Scale: Admission to Discharge



RESULTS (continued)

Vital Signs	Normal	INK	DHE	VPA
Systolic BP max**	120	119.9 (101-148)	119 (96-152)	115.1 (100-137)
Systolic BP min**	90	106.8 (66-139)	113.6 (94-138)	111.6 (94-137)
Diastolic BP max**	90	79.5 (52-97)	76.6 (62-91)	**68.4 (54-81)***
Diastolic BP min**	70	65.6 (49-83)	69 (52-91)	65.2 (51-81)
HR max†	100	86.6 (65-111)	78.8 (55-127)	80.5 (55-120)
HR min†	60	72.9 (56-97)	71.4 (53-109)	75.2 (55-120)
RR max‡	17	19.4 (14-27)	19.1 (16-25)	18.2 (14-24)
RR min‡	11	15.8 (12-20)	16.6 (14-20)	17.3 (13-20)

**p<0.05; ** mmHg; † beats/minute; ‡ breaths/minute*

Patient Reported Side Effects	INK	DHE	VPA	p-value
Dysphoria	1 (4.5%)	0	0	NS
Flush/feel hot	1 (4.5%)	0	0	NS
Nausea	0	1 (6.3%)	0	NS

No instances of dizziness, injection site reactions, rash, or visual disturbances

STRENGTHS AND LIMITATIONS

Strengths
- First study comparing the efficacy of INK to DHE and VPA
- One of the largest reports comparing treatment options for pediatric migraine

Limitations
- Retrospective
- Non-standardized treatment protocol
- Small sample for each treatment group
- Difficult to discern if some adverse reactions are due to pain or medication side effect

CONCLUSIONS

In this small cohort, INK had a **similar response rate and percent pain reduction** compared to DHE and to VPA without the need for IV access or premedication. These results support consideration of INK for abortive migraine treatment, particularly when DHE or VPA may be contraindicated. Larger, randomized controlled trials are warranted to substantiate INK's integration into pediatric migraine treatment.

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