A randomized controlled trial of intranasal ketamine in migraine with prolonged aura

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ABSTRACT

Objective: The aim of our study was to test the hypothesis that ketamine would affect aura in a randomized controlled double-blind trial, and thus to provide direct evidence for the role of glutamatergic transmission in human aura.

Methods: We performed a double-blinded, randomized parallel-group controlled study investigating the effect of 25 mg intranasal ketamine on migraine with prolonged aura in 30 migraineurs using 2 mg intranasal midazolam as an active control. Each subject recorded data from 3 episodes of migraine.

Results: Eighteen subjects completed the study. Ketamine reduced the severity ($p = 0.032$) but not duration of aura in this group, whereas midazolam had no effect.

Conclusions: These data provide translational evidence for the potential importance of glutamatergic mechanisms in migraine aura and offer a pharmacologic parallel between animal experimental work on cortical spreading depression and the clinical problem.

Classification of evidence: This study provides Class III evidence that intranasal ketamine is effective in reducing aura severity in patients with migraine with prolonged aura. ***Neurology***® **2013;80:642–647**

GLOSSARY

CSD = cortical spreading depression.

The aura phase of migraine is present in approximately 20%–30% of migraineurs.[1–4] The most common aura symptoms are visual. Other symptoms include paresthesia, dysarthria, dysphasia, weakness, ataxia, and altered consciousness. The mean duration of aura was documented in one study as 27 minutes.[2] However, some migraineurs, often those with familial or sporadic hemiplegic migraine, have migraine with prolonged aura (International Classification of Headache Disorders–I),[5] where the aura lasts longer than 1 hour and can cause disability for hours or days.

Aura is thought to be the clinical correlate of cortical spreading depression (CSD), first described by Leao.[6] CSD is an electrophysiologic phenomenon producing a slowly (2–6 mm/min) propagating wave of neuronal depolarization followed by a suppression of neural activity.[7] Evidence linking CSD and aura has been provided by fMRI[8] and magnetoencephalography[9] studies. In a knock-in mouse model carrying one of the human mutations for familial hemiplegic migraine (*CACNA1A*-R192Q), the mice had a reduced threshold and increased velocity of CSD.[10]

Currently there is no reliable therapeutic agent to abort the aura phase of the migraine. There have been isolated case reports where drugs appear to have aborted migraine aura[11–15]; none of these studies was controlled. A small open-label study of ketamine suggested that ketamine may reduce the severity and duration of aura in humans.[16] Ketamine has been shown to block CSD in animals[17] and its effect on aura is a test of the CSD–aura link.

METHODS

We chose midazolam as the active control in order to keep blinding intact in the face of the known psychotropic adverse event profile of ketamine. We asked all patients to treat 3 attacks with the nasal spray (either ketamine or midazolam), and also to record

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Table 1 Chart for data recording

Date/time:	
Attack starts:	
Attack ends (back to normal):	
+ Spray:	
1. Muscle power:	
Arm/hand	0 Normal
	1 Mild weakness (able to lift cup to mouth)
	2 Moderate/severe weakness
	3 No movement
Leg	0 Normal
	1 Mild weakness: able to bear weight unaided
	2 Moderate/severe weakness: unable to bear weight on leg
	3 No movement
Face	0 Normal
	1 Facial droop on smiling
	2 Facial droop at rest
	3 No movement
2. Speech	0 Normal
	1 Slight abnormality
	2 Difficult making oneself understood
	3 No speech
	Describe: slurred/unable to get words out
3. Visual disturbance	0 Normal
	1 Slight disturbance
	2 Marked disturbance
	3 Unable to see
	Describe: double vision/lights/patterns
4. Incoordination of hands	0 No symptoms
	1 Mild clumsiness of hands
	2 Moderate clumsiness
	3 Severe clumsiness: incapacitating
5. Loss of feeling	0 Normal
	1 Slight odd sensation/tingling
	2 Definite difference in feeling
	3 Complete numbness
6. Drunken gait	0 Normal walk
	1 Able to walk straight (heel-to-toe) with few wobbles
	2 Unable to walk in straight line heel-to-toe
	3 Unable to maintain balance in standing position
7. Headache	0 None
	1 Mild
	2 Moderate
	3 Severe
8. Conscious level	Normal/altered
Medication and time taken	

the subsequent 3 untreated attacks given the well-described variability in aura from attack to attack.[18] We did not attempt to blind the 3 subsequent attacks since the psychotropic effects of this render the data no longer useful.

Patients and entry criteria. Over a 2-year period, we recruited 30 subjects with migraine with prolonged aura, defined as attacks of aura usually lasting longer than 1 hour and less than 7 days.[5] These patients would be classified as hemiplegic migraine or migraine with probable aura by the second edition of the International Classification of Headache Disorders.[19] None of the patients were related and all had been fully investigated with blood tests and imaging for secondary mimics of aura. We selected subjects with aura duration of at least 3 hours for this study to minimize a placebo response that might be seen if the duration of the aura symptoms was too short. The progression of the aura from onset to maximal disability had to be of duration of greater than 10 minutes as one hypothesis was that ketamine would stop aura progression.

Exclusion criteria. Pregnant women and patients with asthma, cardiac disorders, or psychiatric disorders were excluded. Patients were not allowed to use triptans or ergotamine during the study but simple analgesics were permitted. Migraine prophylaxis was permitted as long as there were no dose changes for 1 month before and then during the study.

Standard protocol approvals, registrations, and patient consents. The study was approved by the joint Ethics Committee of the National Hospital for Neurology and Neurosurgery (UCLH NHS Trust) and the Institute of Neurology (UCL), London, UK.

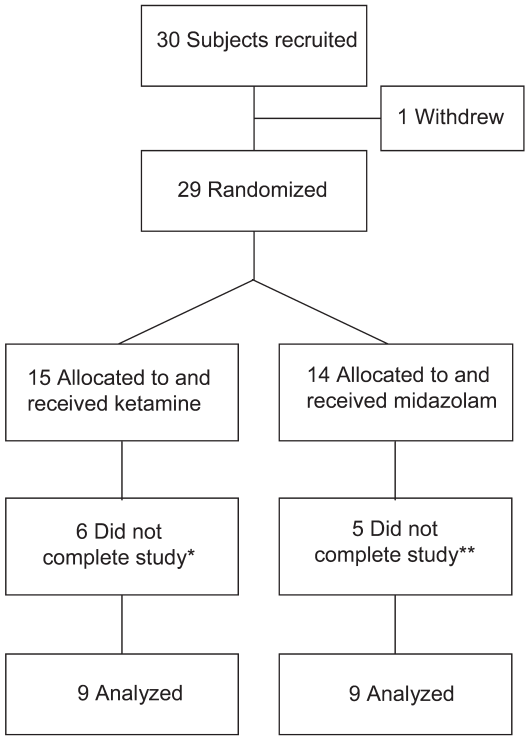
Randomization and administration. Patients were randomized by the pharmacist using a computer-generated program to either ketamine or midazolam. The study was double-blind in both the inpatient and the outpatient arms. Both treatments were administered in identical containers in the form of a nasal spray (25 mg ketamine or 2 mg midazolam). The subjects were assessed prior to commencement of the study and instructed how to administer the spray. The subjects, and in many cases a partner, were instructed on how to record the data. A 2-arm study, inpatient and outpatient, was employed for safety considerations.

Inpatient arm. Patients were invited to attend the hospital for the initial treatment administration. Baseline blood pressure, heart rate, and oxygen saturation were recorded and subjects were observed for 1 hour following administration of the spray. Any adverse effects were noted.

Outpatient arm. Patients were discharged at the conclusion of the inpatient arm. They were instructed to record data during 3 attacks with the spray and 3 without the spray. They were told to take the spray at the very onset of the aura and to continue recording data until the aura had disappeared. The data were recorded every half-hour during the aura (table 1). Patients were asked to note any adverse effects.

Data analysis. Patients reported both duration in hours of their aura and severity of the aura on a mild, moderate, and severe scale, where headache score made no contribution. Severe equaled no movement for a motor symptom. The composite severity scale is reported as the outcome measure and used for testing. As an exploratory study, we set the primary endpoint as a reduction in either length or severity of aura comparing the 3 active with the 3 placebo-treated attacks in the ketamine vs midazolam arms. Data are presented as median and quartile ranges for both the interval scale measure of hours and the ordinal scale severity

Figure CONSORT diagram



*Six patients did not provide endpoint data. **Five patients did not provide endpoint data.

measurement, unless otherwise stated. Severity score and the attack duration were analyzed separately. We did not test for a difference between ketamine and midazolam directly, since midazolam was included for blinding; given the rarity of the syndrome, it was not realistic to power for such a comparison. To assess the results across the attacks without assuming normality of the dependent variables, we used the generalized linear modeling approach, specifically generalized estimating equations, because the study data were captured longitudinally.[20,21] Severity score and duration as dependent variables were considered as ordinal with a multinomial distribution, with the nominal active or placebo treatment variable and the ordinal attack number, as within-subject variables, fitted with a logistic link function with the working correlation matrix structure being independent (SPSS v 17). A 5% level of significance was used for evaluation.

RESULTS Four men and 14 women completed the study, with 9 subjects in each group. The age range was 18–55 years, with a mean age of 35 and 39 in the ketamine and midazolam groups, respectively (figure). Four were taking preventives (valproate, propranolol, flunarizine, pizotifen) and did not alter the dose throughout the study. In some subjects the attack frequency was too low for them to want to take preventives. Many of the other subjects had been on preventives in the past but had not had a good response. Seven subjects in the midazolam group and 5 in the ketamine group used simple analgesics (ibuprofen, paracetamol/acetaminophen) during the study. Attack frequency ranged from weekly to every 3 months and the clinical details are included in table 2. During the study, the median duration of aura without treatment in the 18 subjects was 23 hours (quartile range 3–252): 30 (18–72) hours in the ketamine group and 13 (6–31) hours in the midazolam group. The median severity score without treatment in the ketamine group was 9.5 and in the midazolam group it was 11.

Inpatient safety arm. All patients treated with either midazolam or ketamine tolerated the therapy and went on to the efficacy phase of the study.

Outpatient efficacy arm: Aura. At the primary endpoint, the median difference in duration of attacks was 3 hours (2 to 46; n = 9) shorter with ketamine. Similarly, the median duration of attack in the midazolam-treated patients was also reduced by 3 hours (0 to 15; n = 9). In the ketamine arm, the difference in attack severity was 1.5 (−0.5 to 2.5; n = 9) on the clinical severity scale, suggesting that the baseline attack was worse than the treated attack. In the midazolam group, the difference was a −0.5 (−0.7 to 1.5; n = 9) change, suggesting that the attack was no different on treatment. The severity scoring was a composite measurement reflecting all types of aura listed in table 1.

Modeling the effect of ketamine and midazolam. Given the difference in attack severity, we modeled the outcome across attacks, testing the effect of the treatment. The severity score was significantly affected by ketamine compared to placebo (Wald $\chi^2_1 = 4.6$, $p = 0.032$), whereas attack order was not significant ($\chi 21 = 0.8$, $p = 0.36$). In the midazolam group, the severity score was not significantly altered ($\chi^2_1 = 1.6$, $p = 0.2$).

Outpatient efficacy arm: Headache. Data on headache was incomplete in 10 subjects and showed no clear effect on pain for either treatment. This was partly because subjects were asked to concentrate on aura symptoms and therefore some stopped collecting data when the aura subsided even if headache was still present. Data were only included from attacks where no analgesics were used. Analgesics were used in 7 subjects, although not in all of their attacks.

Adverse effects. Both drugs were tolerated very well. In the ketamine group, 5 subjects described feelings of unreality, euphoria, or mild giddiness temporarily. In the midazolam group, 4 subjects reported transient sedation or giddiness. The effects wore off after 30–45 minutes.

DISCUSSION This randomized parallel group active comparator controlled study in migraine with prolonged aura demonstrates for the first time a reduction in clinical severity of prolonged migraine aura with ketamine. No difference in aura length was reported between treated and untreated attacks in either the

Table 2 Clinical characteristics of the patient cohort

Patient ID	Age, y	Sex	Duration of migraine aura history, y	Attacks, no./y	Aura type				
					Motor	Sensory	Speech	Visual	Other[a]
Ketamine									
1[b]	33	F	1	52	+	+		+	
2[b]	38	F	11	12	+	+	+	+	
3[b]	48	F	20	52	+	+		+	
4[b]	29	F	19	24	+	+	+	+	+3
5[b]	37	F	18	6	+	+	+	+	
6[b]	45	F	20	30	+	+			+1
7[b]	47	F	35	9	+	+		+	+1
8[c]	22	M	4	4	+	+	+	+	+3
9	18	M	3	6					+2
Midazolam									
1	38	F	30	52			+	+	
2[b]	39	M	30	6	+	+		+	
3[d]	43	F	8	8	+	+	+	+	+3
4	57	F	49	52		+	+		
5[c]	33	M	16	24	+	+	+	+	
6[b]	33	F	20	12	+	+	+	+	
7[b]	38	F	2	12	+	+	+		
8[b]	41	F	25	12	+	+	+	+	
9[b]	32	F	17	24	+			+	

[a] 1 = Loss of consciousness; 2 = vertigo, ataxia; 3 = confusion.
[b] Sporadic hemiplegic migraine.
[c] Familial hemiplegic migraine.
[d] Adopted.

ketamine or midazolam arms. However, comparing attack severity, ketamine reduced severity in a clinically meaningful fashion, whereas midazolam did not. The data add clinical, translational evidence to support the notion that glutamatergic mechanisms may be important in the expression of the migraine aura.

Ketamine is a phencyclidine derivative used in humans for its analgesic and anesthetic properties since the 1960s. It is an antagonist of the NMDA glutamate receptor, among other actions including HCN1 hyperpolarizing cation channels,[22] dopaminergic, and opioid effects.[23] The major limiting factor in its use has been its psychomimetic effects. The intranasal route has been shown to be safe and effective.[24,25] In a placebo-controlled study, doses of 10–50 mg of intranasal ketamine were shown to be safe and effective for the treatment of breakthrough pain in chronic pain patients. In this study, 50% of patients reported side effects similar to those seen in our study.[26] The relatively mild psychomimetic effects in our study are unlikely to have had any significant influence on the overall severity ratings since they were very transient, lasting 30–45 minutes. The aforementioned study also demonstrated that plasma levels of ketamine were detectable at 2 minutes, reaching a peak at 30 minutes.[26] Moreover, with IV ketamine at a dose of 0.084 mg/kg, we have seen only minimal cognitive effects in healthy controls.[27] Taken together, the data suggest ketamine can be used in clinically appropriate settings in outpatients.

From a clinical trial design viewpoint, the use of ketamine presents some challenges. We wished to conduct the treatment ultimately in outpatients to capture spontaneous attacks of migraine with aura. Moreover, patients with prolonged aura, particularly with motor impairment, have reduced mobility, making attending for an inpatient study impractical. We sought to mitigate concerns about outpatient use by first having an inpatient safety arm. This involved blinded administration of the treatment interictally. We saw no clinically important issues with regard to cardiorespiratory adverse effects. Having reasoned the inpatient safety arm was necessary, the issue of blinding became more crucial. Given the psychoactive side effects of ketamine, it seemed a subsequent outpatient placebo-controlled treatment either as a parallel-group study or a crossover study would be in effect unblinded. Informed consent, however well written, and the Internet, are powerful potential unblinding tools. We reasoned midazolam would provide a sufficient psychoactive positive blinding to patients who had never had ketamine. The primary comparison was therefore to explore a difference between active treatments. The study does not exclude an active effect of midazolam. We cannot exclude the 3-hour reduction in attack length in both groups is not a pharmacologic effect, although it seems likely the lack of a severity effect of midazolam is a real result. Moreover, given the clinical data we collected, a further limitation is the weighting of the outcome for motor symptoms. This would only be an issue mechanistically if it were considered varying aura symptoms, such as motor vs sensory, would have different pharmacologic or physiologic mechanisms; this seems unlikely and there was no clear evidence of this in our study.

CSD has been characterized to involve neuronal depolarization followed by a suppression of neural activity with an initial cellular efflux of potassium leading to activation of the NMDA channel with glutamate release.[7] The subsequent energy-dependent restitution of ion gradients eventually restores normal neuronal activity. In animal studies glutamate NMDA receptor antagonists, including ketamine, have been consistently shown to block CSD.[17,28–31] The same cannot be said for other drugs used in migraine such as triptans or tetracyclic ergoline derivatives.[31] Sumatriptan does not affect the initiation or duration of CSD but may have some effect on later cerebrovascular changes.[32] We are not aware of any

evidence that midazolam has any effect on CSD. Ketamine has also been shown to increase cerebral blood flow in humans[33] and accelerate the restitution of neuronal function after hypoxia in rats.[34] The clinical data here thus support a role for NMDA activation in migraine aura as has been predicted from the basic experimental studies. The data do not exclude other pharmacologic targets, although importantly the data support the translational use of the CSD model to develop antimigraine aura therapeutics.

An open-label study[16] demonstrated a beneficial response in terms of duration and severity of aura in 5 of 11 subjects. This study was in contrast to triptan administration, either sumatriptan subcutaneously[35] or eletriptan orally,[36] administered during migraine aura, which neither shortened aura nor prevented headache. Our study did not demonstrate a significant effect on aura duration. One possibility which needs to be explored is the dose-effect response. Although the 25 mg ketamine dose used in our study was the same as that used in the aforementioned study,[16] doses of up to 50 mg have been used in a previous study.[26] Some patients may require higher doses for a therapeutic effect. Another possible reason for a nonsignificant effect on aura duration may be the difference in the median duration of aura pretreatment in the 2 groups, which was 30 hours in the ketamine group and 13 hours in the midazolam group. This occurred despite randomization and thus the lack of effect on duration may have been a false-negative result with underpowering in the context of the non-normal distribution of the endpoints employed.

Our study suggests that ketamine may be useful in a select group of migraineurs with prolonged aura. The data support a view that the attack is rendered less severe, and this effect is clinically meaningful based on the patients' comments and our clinical experience. The design of the study does not exclude an effect of midazolam, although for both substances study design to preserve blinding remains a very significant issue, and midazolam has no effect on CSD of which we are aware. Further studies may require higher doses of ketamine, more patients, or more attacks. Patients with prolonged aura are relatively rare, so large-scale studies are a significant challenge. At this time, patients with prolonged aura have no controlled trial–proven strategies for the treatment of their attacks. Intranasal ketamine 25 mg is a safe and effective treatment for prolonged aura that is useful for patients and provides support for glutamatergic hypotheses around migraine and its relationship to CSD. The new data are consistent with the recent demonstration of an association of an allele flanked by genes regulating glutamate in a large genome-wide association study[37] that is again broadly consistent with an important role for glutamatergic mechanisms at least in migraine aura. Our study does not endorse the widespread use of ketamine in migraine aura, although it does provide data supporting the glutamate hypothesis in aura and thus provides a further impetus to the development of novel therapeutics[38] for the treatment of this often disabling symptom.

AUTHOR CONTRIBUTIONS

Drs. Kaube and Goadsby conceived the study. Drs. Afridi, Giffin, Kaube, and Goadsby contributed to the design and execution. Dr. Afridi collated the data and Dr. Goadsby ran the analysis. All authors participated in manuscript revision.

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DISCLOSURE

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