ANESTHESIOLOGY

Dissociative and Analgesic Properties of Ketamine Are Independent

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ANESTHESIOLOGY 2020; 133:1021–8

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Ketamine produces analgesia and dissociation at low doses
- Ketamine's analgesic properties have been suggested to result from its dissociative properties
- Midazolam is typically administered to treat ketamine-induced dissociative symptoms

What This Article Tells Us That Is New

- The hypothesis that the dissociative and analgesic properties of ketamine are independent was tested in healthy subjects that received 2 mg/kg ketamine, and then, 2 mg of midazolam at a later timepoint
- Ketamine-induced analgesia had no strong inherent relationship with ketamine-induced dissociation beyond being independently modulated by ketamine

ABSTRACT

Background: Ketamine is a dissociative anesthetic with analgesic properties. Ketamine's analgesic properties have been suggested to result from its dissociative properties. To the authors' knowledge, this postulate is unsubstantiated. The authors hypothesize that the dissociative and analgesic properties of ketamine are independent.

Methods: The authors conducted a single-site, open-label study of ketamine anesthesia (2 mg/kg) in 15 healthy subjects. Midazolam was administered at a prespecified time point to attenuate dissociation. The authors longitudinally assessed precalibrated cuff pain intensity and quality using Patient-Reported Outcomes Measurement Information System questionnaires, and dissociation, using the Clinician Administered Dissociative States Scale. Mixed effects models were used to assess whether dissociation accounted for the effect of ketamine on pain intensity and quality.

Results: The dissociation model demonstrated an inverted U-shaped quadratic relationship between time and dissociation scores. Additive to this effect, midazolam reduced the dissociation adjusted means by 10.3 points (95% CI, 3.4 to 17.1; $P = 0.005$). The pain intensity model also demonstrated a U-shaped quadratic relationship between time and pain intensity. When the pain intensity model was reanalyzed with dissociation scores as an additional covariate, the dissociation term was not retained in the model, and the other effects were preserved in direction and strength. This result was conserved for nociceptive and neuropathic pain quality.

Conclusions: Ketamine's analgesic properties are not exclusively caused by dissociation. Thus, ketamine may be used as a probe to advance our knowledge of dissociation independent neural circuits that encode pain.

(ANESTHESIOLOGY 2020; 133:1021–8)

KETAMINE is a phencyclidine analog with anesthetic and analgesic properties.[1–4] At low doses, ketamine is associated with analgesia and dissociative symptoms, and at higher doses, it is associated with loss of responsiveness.[5,6] Dissociative symptoms are characterized by distortion of visual and auditory stimuli, and feelings of detachment from the environment and self. The channel blocking activity of ketamine at *N*-methyl-D-aspartate (NMDA) receptors may partly explain these dissociative symptoms.[7] This is because NMDA receptor blockade is associated with markedly dysregulated pyramidal neuronal activity that manifests as electroencephalogram high frequency oscillations when ketamine is administered alone[5,6] or as a part of a balanced general anesthetic technique.[8–10] Ketamine also interacts with hyperpolarization-activated cyclic nucleotide-gated 1 channels and opioid, monoaminergic, cholinergic, nicotinic, and muscarinic receptors.[11,12]

The dissociative properties of ketamine have limited its widespread use as an analgesic medication. A recent consensus guideline for the use of intravenous ketamine in acute pain management explicitly states that ketamine's profound analgesic properties are intricately bound to its dissociative properties.[13] This line of reasoning is largely supported by the following: (1) NMDA receptor–mediated activity plays a key role in sensory information processing;

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 970. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract available in the online version.

Submitted for publication January 31, 2020. Accepted for publication July 31, 2020. Published online first on September 8, 2020. From the Departments of Anesthesia, Critical Care, and Pain Medicine (J.G., S.C., B.R.E., J.C.P., E.Y.H., R.I., J.M., K.M.C., J.Q., O.A.) and Neurology (J.J.L.), Massachusetts General Hospital, Boston, Massachusetts; Department of Anesthesiology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile (J.C.P.); and Henry and Allison McCance Center for Brain Health, Massachusetts General Hospital, Boston, Massachusetts (O.A.).

 Anesthesiology 2020; 133:1021–8. DOI: 10.1097/ALN.0000000000003529

<zdoi;. DOI: 10.1097/ALN.0000000000003529>

and (2) analgesia and dissociation are both considered states of altered sensory perception, implying a common mechanistic basis.[14,15] To our knowledge, the viewpoint that ketamine's analgesic properties are caused by its dissociative properties has not been investigated. Thus, the analgesic and dissociative properties of ketamine analgesia may be independent. This insight may benefit future investigations of ketamine analgesia and neural circuits that encode pain in humans.

Therefore, we conducted a single-site, open-label study of ketamine anesthesia (2 mg/kg) in 15 healthy subjects. Benzodiazepines are typically administered to treat ketamine-induced dissociative symptoms.[15] Therefore, we administered midazolam at a prespecified time point to facilitate disentangling analgesic and dissociative drug properties. We longitudinally assessed precalibrated cuff pain intensity and quality using Patient-Reported Outcomes Measurement Information System pain intensity and quality questionnaires, and dissociation, using the Clinician Administered Dissociative States Scale.[16] We hypothesized that the dissociative and analgesic properties of ketamine are independent.

Materials and Methods

The Partners Institutional Review Board (Boston, Massachusetts) approved this human research study (2018P000417). The data analyzed in this article were acquired during an electroencephalogram study of ketamine general anesthesia that was registered on www.ClinicalTrials.gov (NCT03553758). Data from this study have not previously been published.

Subject Recruitment

Subjects were recruited and data collected between September 2018 and January 2019. Subjects underwent a complete medical history and a preanesthesia assessment. The primary inclusion criterion was meeting American Society of Anesthesiology Physical Status I. Key criteria for exclusion were pregnancy, personal or family history of anesthesia-related complications, suspected history of drug abuse, and neuropsychiatric diagnoses. We performed the following screening laboratory tests: complete blood count, liver function, basic metabolic panel, urine toxicology, and urine pregnancy for females. We also recorded data from a 12-lead electrocardiogram.

Study Design

This was a single-site, open-label study of ketamine anesthesia in 15 healthy subjects. Figure 1 is an illustration of the study design. All study procedures were conducted at the Massachusetts General Hospital (Boston, Massachusetts). Subjects were required to avoid food and water intake for at least 8 h before study onset. We performed urine toxicology and pregnancy testing before the administration of ketamine. We monitored blood pressure using a standard noninvasive pneumatic cuff, oxygen saturation using pulse oximetry, ventilation using capnography, and cardiac rhythm using a 5-lead electrocardiogram.

We rapidly (~1 min) administered a bolus dose of intravenous ketamine (2 mg/kg) to 15 subjects and assessed pain and dissociation measures intermittently. The first assessment (pain and dissociation measures) occurred after cuff pain calibration and before the administration of ketamine. The second assessment (pain measures) occurred approximately 30 min after the administration of ketamine. The third assessment (pain and dissociation measures) occurred approximately 60 min after the administration of ketamine. After the third assessment, we administered 2 mg of midazolam to attenuate ketamine associated dissociation. The fourth assessment (pain and dissociation measures) occurred approximately 75 min after the administration of ketamine. The fifth assessment (pain and dissociation measures) occurred approximately 120 min after the administration of ketamine. One subject did not perform assessments after recovery of responsiveness. Therefore, data from 14 subjects were analyzed. Of these data, only one dissociative measure datapoint was missing.

The airway was not instrumented, and all subjects breathed spontaneously throughout the study protocol without assistance. Supplemental oxygen was provided using a face mask. A board-certified anesthesiologist was present during all study procedures.

Pain and Dissociation Measures

Patient-Reported Outcomes Measurement Information System questions were used to assess for pain intensity and quality associated with the cuff pain stimulus. The National Institutes of Health Common Fund's Patient-Reported Outcomes Measurement Information System was designed to provide patient reported outcome measurement tools developed using advances in information technology, psychometrics, and qualitative, cognitive, and health survey research to measure outcomes such as pain.[17] Patient-Reported Outcomes Measurement Information System measures are normalized to a standardized t-distribution (https://www.assessmentcenter.net/ac_scoringservice; accessed December 20, 2019). The standard t-score mean for Patient-Reported Outcomes Measurement Information System questionnaires is 50 for the population, with an SD of 10. Higher scores indicate more of the concept being measured.

We assessed pain measured using the following questionnaires: Pain Intensity 1A–Numeric Rating Scale (v1.0), Neuropathic Pain Quality 5a (v2.0), and Nociceptive Pain Quality 5a (v2.0). All subjects first underwent baseline pain stimuli calibration using a validated pneumatic cuff pain device (Hokanson Rapid Cuff Inflator; Hokanson E20, D. E. Hokanson, Inc., USA),[18–20] calibrated to 7 out of 10 pain using the Pain Intensity 1A–Numeric Rating Scale (v1.0). This device, which primarily elicits pain sensitivity in muscle and other deep tissues,[18] uses a computer-controlled

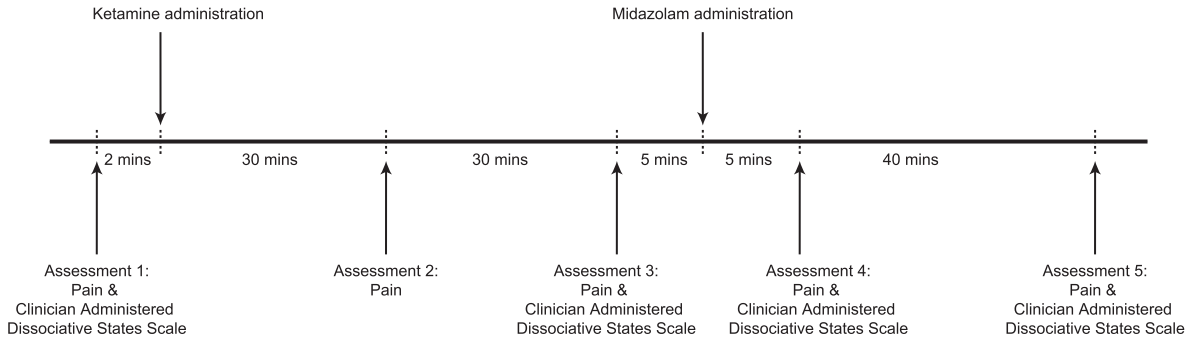

Fig. 1. Schematic of the study protocol. We acquired data using an open-label and single-site study design in (n = 15) healthy subjects. Subjects were induced to lose responsiveness with 2 mg/kg of intravenous ketamine. We also administered 2 mg of intravenous midazolam to attenuate ketamine-induced dissociation. We assessed pain intensity and quality using Patient-Reported Outcomes Measurement Information System questionnaires and dissociative symptoms using the Clinician Administered Dissociative States Scale.

air compressor to inflate and maintain the cuff to a prespecified pressure. The cuff pain stimulus was delivered to the gastrocnemius area of the lower leg.

We assessed for dissociation using the Clinician Administered Dissociative States Scale, which was developed to measure perceptual, behavioral, and attentional alterations during dissociative experiences.[16] Higher Clinician Administered Dissociative States Scale scores indicate more of the concept being measured.

Statistical Methods

We did not perform an *a priori* sample size calculation. Data and statistical analyses plans were defined and written after the data were accessed. Patient characteristics are presented as mean ± SD. We ran a variation of a limited backward elimination mixed random and fixed effects longitudinal analysis.[21] Mixed effects models are commonly used for longitudinal analysis and contain a mixture of the standard fixed predictors and "random" terms such as subjects whose effects are not of interest *per se* but necessary to include to correctly account for correlated error variance, in this case within the same subject. All *P* values were computed based on the two-sided tests. Significance level was set at 0.05. The fixed covariate of primary interest was the quadratic effect of time (minutes post–ketamine administration). By construct, the lower order effect of time was also included as a covariate. Additional subject-level fixed covariates were sex, age, and ketamine dose (mg). Random terms were subject intercepts and the interaction of subjects with time, which were allowed to be correlated.

An initial model including all the aforementioned terms was run, as well as a limited backward elimination model excluding sequentially the least significant term ($P > 0.2$) until only significant terms remained or nonsignificant terms subsumed within significant higher-order terms. The above model was run separately for each of the dependent variables: Patient-Reported Outcomes Measurement Information System Pain Intensity, Patient-Reported Outcomes Measurement Information System Neuropathic Pain, Patient-Reported Outcomes Measurement Information System Nociceptive Pain, and Clinician Administered Dissociative States Scale. A time-varying fixed binary covariate of premidazolam *versus* postmidazolam was included in the Clinician Administered Dissociative States Scale model. Further models were run in which each pain measure was the dependent variable but with an additional covariate assessing dissociation to assess the possible role of dissociation in mediating the effects of ketamine on pain. Relevant differences in least squares means estimates (*i.e.*, midazolam, sex) in the final models were reported as adjusted means. Residuals from all fit models were examined for conformance to assumptions of normality. JMP Pro 14 (USA) was the statistical software employed for all analyses.

Results

We obtained written informed consent from 15 subjects (8 males), age 24 ± 3.4 yr, mean weight 70 ± 12 kg, and mean body mass index 23.5 ± 2.4 kg/m^2. Results from Patient-Reported Outcomes Measurement Information System and Clinician Administered Dissociative States Scale assessments are summarized in table 1.

Pain Intensity and Dissociation Are Independently Modulated by Ketamine

First, we assessed for differences in dissociation scores. The final backward elimination model (sex, age, and ketamine dose were eliminated) demonstrated an inverted U-shaped quadratic relationship between time and dissociation (fig. 2A). The shape of this curvilinear relation was disrupted and lowered by the additive effect of midazolam at the point it was administered (fig. 2A). Midazolam reduced the dissociation adjusted means by 10.3 (95% CI, 3.4 to

Table 1. Pain and Dissociation Scores

	Preketamine	~30 min Postketamine	~60 min Postketamine	~75 min Postketamine; ~15 min Postmidazolam	~120 min Postketamine; ~60 min Postmidazolam
Clinician Administered Dissociation States Score, mean ± SD	0.2 ± 0.4	N/A	22.1 ± 17	14.3 ± 11.6	5.2 ± 7.3
Pain intensity, mean ± SD	7.9 ± 0.5	1.6 ± 1.6	4.1± 2.2	4.3 ± 2.2	5.4 ± 2.3
Nociceptive pain, mean ± SD	50.6 ± 9.4	37.2 ± 8.6	41.2 ± 7.6	43.7 ± 9.6	47 ± 10.7
Neuropathic pain, mean ± SD	47.9 ± 5.6	39.9 ± 3.8	44.7 ± 4.6	43.7 ± 5	44.4 ± 6.4

17.1; $P = 0.005$) (table 2). Residuals from this model and all those below did not differ markedly from normality.

Next, we assessed for differences in pain intensity scores. The final backward elimination model (sex, age, and ketamine dose were eliminated) demonstrated a U-shaped quadratic relationship between time and pain intensity (fig. 2B; table 2) with a minimum value at approximately 60 min postketamine. When this final pain intensity model was rerun with the dissociation term as an additional covariate, it was not retained in our model. When the dissociation term was included in the initial model for pain intensity, it was the first term removed in the backward elimination algorithm. These findings suggest that the effect of ketamine in reducing pain intensity scores is not exclusively caused by dissociation.

Nociceptive Pain Quality and Dissociation Are Independently Modulated by Ketamine

The final nociceptive pain quality backward elimination model (sex, age, and ketamine dose were eliminated) demonstrated a U-shaped quadratic relationship between time and nociceptive pain quality (fig. 2C; table 2). Similar to the pain intensity model, when the final nociceptive pain quality model was rerun with the dissociation term as an additional covariate, it was not retained in our model. When the dissociation term was included in the initial model for nociceptive pain quality, it was the first term removed in the backward elimination algorithm.

Neuropathic Pain Quality and Dissociation Are Independently Modulated by Ketamine

The final neuropathic pain quality backward elimination model (sex and ketamine dose were eliminated) demonstrated a U-shaped quadratic relationship between time and neuropathic pain quality (fig. 2D, table 2).). There was also an additive main effect of sex, whereby a reduction in adjusted means of 4.5 (95% CI, 1 to 7.8; $P = 0.016$) was associated with being female. Similar to the pain intensity and quality models, when the final neuropathic pain quality model was rerun with the dissociation term as an additional covariate, it was not retained in our model. When the dissociation term was included in the initial model for nociceptive pain quality, it was the first term removed in the backward elimination algorithm.

Discussion

In this investigation, we studied whether ketamine-induced analgesia is caused by ketamine-induced dissociation. We confirmed that ketamine is associated with both analgesia and dissociation,[1,2] and that midazolam attenuates ketamine-induced dissociation.[22,23] However, our major finding was that ketamine-induced analgesia had no strong inherent relationship with ketamine-induced dissociation beyond being independently modulated by ketamine. Thus, ketamine or its metabolites modulate distinct neural circuits to produce dissociation and analgesia.

The channel blocking activity of ketamine at NMDA receptors may partly explain its dissociative properties. This is because ketamine blocks excitatory NMDA receptors on fast-spiking cortical interneurons more effectively than those on pyramidal neurons.[24,25] This results in markedly dysregulated pyramidal neuronal activity because the relative inactivity of cortical interneurons leads to glutamate-mediated pyramidal–pyramidal neuronal facilitation. Consistent with this notion, lamotrigine, an antiepileptic medication that reduces cortical glutamate release and pyramidal neuron facilitation, attenuates the dissociative properties of ketamine.[26,27] Similarly, midazolam also reduces pyramidal neuron facilitation by downstream activity resulting from binding at gamma amino-butyric acid receptors on pyramidal neurons. Taken together, our findings suggest that the analgesic mechanisms of ketamine are unlikely to be downstream of ketamine's activity on fast-spiking cortical interneurons or pyramidal–pyramidal neuronal facilitation.

Our results are consistent with a recent report which states that an N-aliphatic analog of ketamine-induced analgesia comparable to ketamine but with considerably less dissociative properties (*i.e.*, analgesia and dissociation are separable).[28] However, the mechanistic underpinnings of ketamine-induced analgesia are not clear. Intrathecal ketamine is associated with a dense motor blockade that precedes sensory blockade to suggest that spinal motor neurons

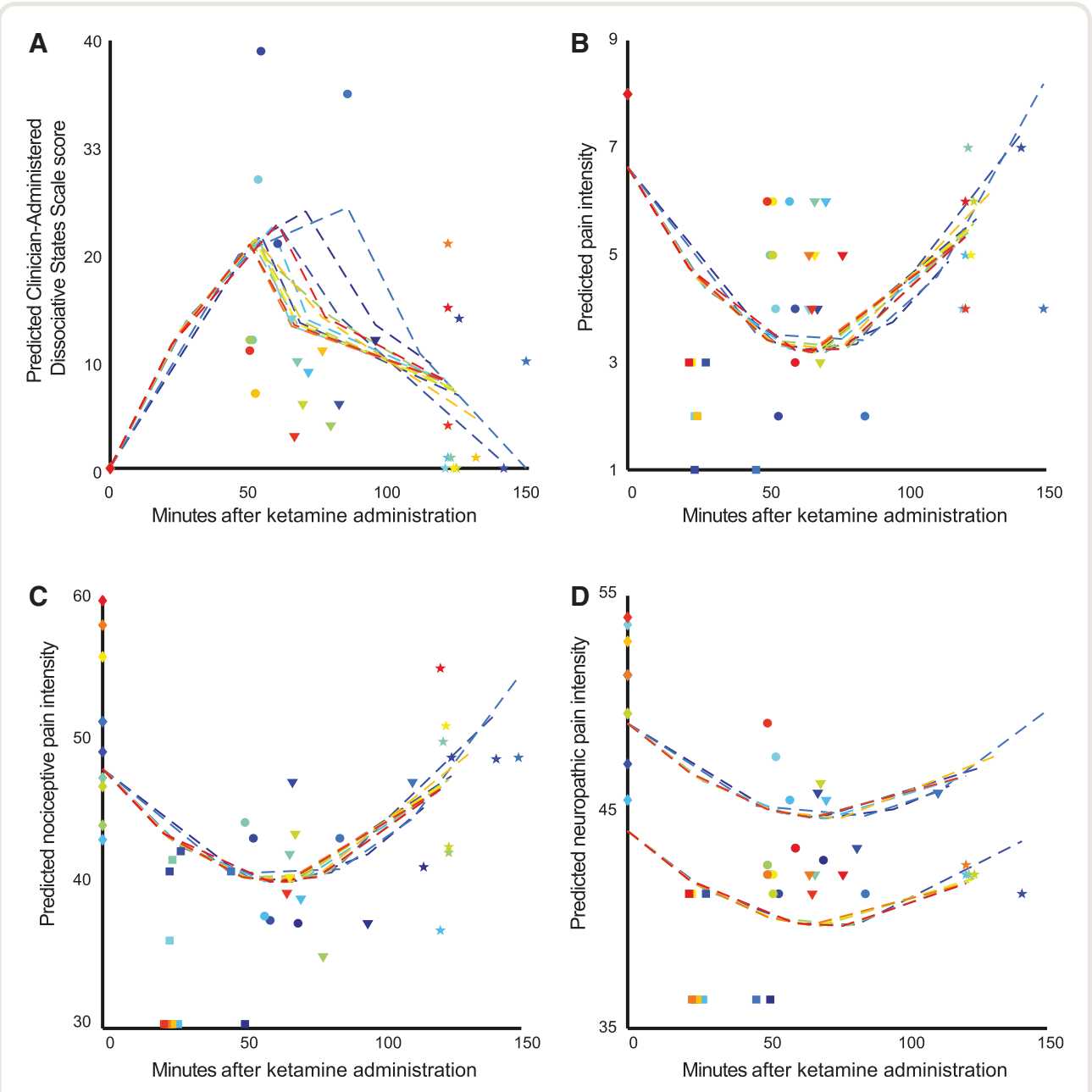

Fig. 2. Raw and predicted data for ketamine induced dissociation and pain measures. Each *dashed line* connects conditional predicted values from the model for the same subject (arbitrary colors are a visual aid to differentiate subjects). Raw values are depicted with markers and aligned with the same color scheme above. Marker shapes are grouped to represent the different assessment periods. (*A*) Illustration of predicted inverted U-shaped quadratic relationship between Clinician Administered Dissociative States Scale and time after ketamine administration. Also apparent in the figure is an attenuating effect of midazolam noticeable after the point of its administration for each subject. The final backward elimination models demonstrated a U-shaped quadratic relation between time and (*B*) pain intensity, (*C*) nociceptive pain, and (*D*) neuropathic pain. The two distinct clusters of trajectories in part *D* illustrate the effect of sex (higher cluster corresponds to males; lower females).

are more sensitive to the effects of ketamine.[29] Intravenous ketamine is not associated with motor blockade. Thus, it is unlikely that acute analgesic properties of ketamine are mediated predominantly by drug activity in the spinal cord. We note that opioids are the mainstay of pain treatment and ketamine interacts with the opioid receptors. Thus, it is reasonable to postulate that ketamine-induced analgesia is mediated through its activity at opioid receptors.[30] However, studies in laboratory models have shown that the analgesic properties of ketamine are unchanged despite

Table 2. Final Backward Elimination Models

Term	Estimate (95% CI)	*P* Value
Clinician Administered Dissociated States Score final model		
Intercept	−10.2 (−19.0, −1.3)	0.026
Midazolam (N)	10.3 (3.4, 17.1)	0.005
Time (min after ketamine)	0.6 (0.5, 0.8)	< 0.0001
Time (min after ketamine) × time (min after ketamine)	−0.004 (−0.01, −0.003)	< 0.0001
Pain intensity final model		
Intercept	6.6 (5.7, 7.6)	< 0.0001
Time (min after ketamine)	−0.1 (−0.1, −0.1)	< 0.0001
Time (min after ketamine) × time (min after ketamine)	0.001 (0.001, 0.001)	< 0.0001
Nociceptive pain final model		
Intercept	48.0 (43.0, 53.0)	< 0.0001
Time (min after ketamine)	−0.3 (−0.4, −0.1)	0.0002
Time (min after ketamine) × time (min after ketamine)	0.002 (0.001, 0.003)	< 0.0001
Neuropathic pain final model		
Intercept	48.7 (45.6, 51.8)	< 0.0001
Time (min after ketamine)	−0.1 (−0.2, −0.02)	0.015
Time (min after ketamine) × time (min after ketamine)	0.001 (0.0001, 0.001)	0.024
Sex (F)	−4.5 (−8.0, −1.0)	0.016

Estimate, unstandardized partial regression coefficient; for midazolam and sex, the estimate represents the difference in adjusted means.

the administration of naloxone, an opioid receptor antagonist.[31,32] This suggests that the analgesic properties of ketamine are unrelated to its activity at opioid receptors.

Bilateral interventions to the locus coeruleus in laboratory models have demonstrated the existence of locus coeruleus–noradrenergic pain circuitry,[33,34] and several lines of evidence suggest that the noradrenergic system is fundamental to ketamine-induced analgesia. First, ketamine is a noncompetitive inhibitor of the norepinephrine transporter, and thus targets locus coeruleus autoreceptors.[35–37] Second, ketamine-induced antinociception was found to be absent after lesion of the spinal dorsolateral funiculus containing descending noradrenergic axons.[38] Third, intrathecal yohimbine, an α_2-adrenoceptor antagonist, has been demonstrated to diminish the analgesic properties of ketamine.[39] Fourth, a correlation between locus coeruleus norepinephrine and ketamine analgesia has been demonstrated in rats with a targeted degeneration of nerve terminal projections originating from the locus coeruleus.[40] Thus, ketamine-induced analgesia may be mediated through locus coeruleus–noradrenergic pain circuitry.

Functional magnetic resonance imaging studies have recently implicated the descending antinociceptive pathway, which is chiefly modulated by monoamines, in ketamine-induced analgesia from neuropathic pain.[41,42] Our current finding is expected to further motivate future studies (*e.g.*, ultra-high field functional magnetic resonance imaging) to elucidate how ketamine acts in the brainstem and cortical circuits to produce neuropathic and nociceptive analgesia. The strengths of our study include the structured and longitudinal pain and dissociation assessments, and pharmacologic modulation of dissociation with midazolam. However, a key limitation is that our study population was healthy without chronic pain disorders (*e.g.*, fibromyalgia). Further, the clinical significance of the sex difference we found in neuropathic pain is unclear. We note that there may be components of dissociation that are not captured by the Clinician Administered Dissociative States Scale. However, our results were conserved when we analyzed amnesia, depersonalization, and derealization subscales of the Clinician Administered Dissociative States Scale (Supplemental Digital Content, http://links.lww.com/ALN/C474). Validating our methodologic approach, and consistent with clinical intuition, midazolam disrupted the shapes of the curvilinear relation of the depersonalization and derealization subscales, but not the amnesia subscale (*i.e.*, midazolam does not reduce amnesia). Further, our sample size was relatively modest. Finally, our inferences may be limited to pneumatic cuff pain. However, cuff pain is preferential to deep tissue nociceptors,[18] and is clinically relevant because most clinical pain originates in deep tissue nociceptors rather than cutaneous nociceptors. and is clinically relevant because most clinical pain originates in deep tissue nociceptors rather than cutaneous nociceptors.

Taken together, our results suggest that the ketamine-induced dissociation and analgesic properties are independent. Thus, ketamine may be used as a probe to advance our knowledge of dissociation independent neural circuits that encode pain.

Research Support

Supported by grant No. RO1AG053582 from the National Institutes of Health National Institute on Aging (Bethesda, Maryland; to Dr. Akeju), innovation funds from the Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital (Boston, Massachusetts;

to Dr. Akeju), and funding from the Department of Anesthesiology, School of Medicine, Pontificia Universidad Católica de Chile (Santiago, Chile; to Dr. Pedemonte).

Competing Interests

Dr. Akeju has received speaker's honoraria from Masimo Corporation (Irvine, California) and is listed as an inventor on pending patents on electroencephalogram monitoring and oral dexmedetomidine that are assigned to Massachusetts General Hospital (Boston, Massachusetts). All other authors declare no competing interests.

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