Ketamine Does Not Increase Cerebral Blood Flow Velocity or Intracranial Pressure During Isoflurane/Nitrous Oxide Anesthesia in Patients Undergoing Craniotomy

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Ketamine's effect on cerebral hemodynamics is controversial. We hypothesized that ketamine would not increase intracranial pressure (ICP) and cerebral blood flow (CBF) velocity in anesthetized, ventilated patients. Twenty patients requiring craniotomy for brain tumor or cerebral aneurysm were studied. After induction with thiopental, anesthesia was maintained with isoflurane and nitrous oxide in oxygen. During controlled ventilation ($Paco_2$ 34 ± 1 mm Hg); middle cerebral artery blood flow velocity (V_{MCA}), mean arterial blood pressure (MAP), bilateral frontooccipital processed electroencephalogram (EEG), and ICP were measured before and for 10 min after intravenous ketamine 1.0 mg/kg. Cerebral arteriovenous oxygen content difference ($AVDo_2$) and cerebral perfusion pressure (CPP) were calculated. After ketamine, MAP, CPP, $Paco_2$, and $AVDo_2$ were unchanged. ICP decreased from 16 ± 1 mm Hg to 14 ± 1 mm Hg (mean ± SE; $P < 0.001$) and V_{MCA} decreased from 44 ± 4 cm/s to 39 ± 4 cm/s ($P < 0.001$). Total EEG power decreased ($P < 0.02$). These results suggest that ketamine can be used in anesthetized, mechanically ventilated patients with mildly increased ICP without adversely altering cerebral hemodynamics.

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The potential adverse effects of ketamine in neurosurgical anesthesia have been well established (1). However, a reexamination of ketamine is warranted because (a) data regarding the effects of ketamine on cerebral hemodynamics are conflicting, (b) the mechanisms responsible for these effects are not well understood, and (c) as a noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist, ketamine may be of benefit to patients at risk of cerebral ischemia.

Ketamine has been considered contraindicated in patients with increased cerebral elastance because of its reported effect on intracranial pressure (ICP) and cerebral blood flow (CBF) (1). Although early experience with ketamine suggested that it may increase ICP in patients with intracranial hypertension (2), it has no effect on ICP in ventilated, head-injured patients (3). Moreover, it decreases CBF (4) and cerebral spinal fluid pressure (CSFP) in anesthetized animals (5). Thus, anesthetics (5,6) and $Paco_2$ appear to influence ketamine's effects on the cerebral vasculature.

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Experimentally, ketamine, a NMDA antagonist, improves neurologic outcome in head trauma (7). Consequently, the use of ketamine and other NMDA antagonists has been proposed for use in humans at risk of cerebral ischemia (8). However, the effects of ketamine on cerebral and systemic hemodynamics during general anesthesia in humans are unknown.

The purpose of our study was to determine the effect of ketamine on cerebral hemodynamics, under controlled conditions, in patients with neurologic disease. We hypothesized that ketamine would not increase ICP or adversely affect cerebral hemodynamics in anesthetized, mechanically ventilated subjects. Accordingly, we studied neurosurgical patients undergoing craniotomy for excision of brain tumor or clipping of cerebral aneurysm.

Methods

The study was approved by our Human Subject Review Committee and informed consent was obtained from each patient. Twenty neurosurgical patients were enrolled in the study: 10 of the patients had

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supratentorial tumors; the rest had intracranial aneurysms. Using the Hunt and Hess (9) classification system for subarachnoid hemorrhage, all patients with aneurysms had Grades of I, II, or III. Although two of the patients in the tumor group had symptoms of increased ICP (headache and nausea), all were conscious and capable of giving consent at the time of recruitment. Their ages and weights were 49 ± 10 yr and 78 ± 18 kg (mean ± SD), respectively.

Monitors included electrocardiography, pulse oximetry, and end-tidal capnometry in all patients. Bilateral frontooccipital electroencephalograms (EEGs) were recorded and processed using aperiodic analysis (Lifescan™ and research program; Diatek, San Diego, CA). Analysis of individual EEG bands, δ (1–4 Hz), α (8–13 Hz), Θ (4–8 Hz), and β (13–30 Hz), as well as the total EEG power were analyzed.

The right middle cerebral artery (MCA) was insonated transtemporally using a transcranial Doppler (CDS; Medasonics, Fremont, CA). The mean blood flow velocity (V_{MCA}) was calculated from the formula: V_{MCA} = [(systolic flow velocity − diastolic flow velocity)/3] + diastolic flow velocity. The technique of V_{MCA} determination using a 2-MHz transcranial Doppler was accomplished as follows. The Doppler probe was anchored using a head harness so that the angle of insonation remained constant throughout the study. Doppler signals from the right MCA were identified and measured at a depth of 45–50 mm. The shift in frequency spectra of the Doppler signal converted into velocity was displayed on a video monitor and peak systolic and diastolic MCA flow velocities in centimeters per second were obtained manually using the cursor to read the average value from two to three cardiac cycles. To eliminate respiratory fluctuations, readings were always taken during the end-expiratory phase.

Additional monitors included an indwelling radial arterial catheter for direct pressure measurement, an ICP monitor (Camino Laboratory, San Diego, CA) or lumbar subarachnoid catheter, and a jugular bulb catheter. Seven patients had lumbar catheters placed to drain CSF as part of their intraoperative management. These catheters were transduced to measure CSFP, which was interpreted to be equivalent to ICP. No patient whose ICP was monitored via lumbar subarachnoid catheter had obstructive hydrocephalus, and a satisfactory wave form was confirmed before commencement of the study. In three tumor patients, neither an ICP monitor nor a lumbar drain was placed and no ICP data were available.

In all patients, a 5.25-in. 16-gauge catheter was inserted into the right internal jugular vein and advanced in a retrograde fashion into the jugular bulb. Radiographic confirmation of a satisfactory position of the jugular bulb catheter was demonstrated in the recovery room in every patient. The tip of the catheter was medial to and within 2 cm of the mastoid process.

No sedative or narcotic medications were administered before induction. Anesthesia was induced with thiopental 4–6 mg/kg and lidocaine 1.5 mg/kg; muscle relaxation was achieved with vecuronium 0.1 mg/kg. After tracheal intubation, the lungs were mechanically ventilated. Anesthesia was maintained with nitrous oxide 50% in oxygen and isoflurane 0.3% to 0.4% (end-tidal). After at least 15 min of stable end-tidal isoflurane, and during mild hypocapnia (34 mm Hg) and stable hemodynamics, baseline measurements were obtained. An intravenous bolus of ketamine (1 mg/kg) was administered. Phenylephrine was administered if the mean arterial blood pressure (MAP) decreased by 15% or more from baseline values.

V_{MCA}, MAP, heart rate (HR), and ICP or CSFP were measured and recorded every minute for 10 min after the administration of ketamine. Analysis of individual EEG bands and the total EEG power were analyzed at 2-min intervals. Simultaneous arterial and jugular venous blood samples were obtained at 0, 5, and 10 min. $AVDo_2$ was calculated according to the following formula: $AVDo_2$ = [Hgb × (Sao_2 − $Sjvo_2$) × 1.39] + [($Paco_2$ − $Pjvo_2$) × 0.003] vol%, where Hgb = hemoglobin concentration, Sao_2 = arterial oxygen saturation, $Sjvo_2$ = jugular bulb oxygen saturation, $Paco_2$ = arterial oxygen partial pressure, $Pjvo_2$ = jugular bulb oxygen partial pressure, and $AVDo_2$ = arteriovenous oxygen content difference. Blood gas partial pressures and hemoglobin oxygen saturation were determined using a Stat Profile 5™ blood gas analyzer (Nova Biomedical, Waltham, MA). The oxygen saturation was calculated automatically by the analyzer using standard equations. Surgical stimulation did not occur until the study was completed.

Data were analyzed using analysis of variance for repeated measures. A P value of < 0.05 was considered significant. When significance was found, Dunnett's test was used for *post-hoc* testing. Values are reported as mean ± SE.

Results

Comparison of all variables measured in the tumor and the aneurysm groups revealed that there were no statistically significant differences between the two groups with the exception of V_{MCA} measurements. Therefore, the results for the aneurysm and tumor groups were combined. The V_{MCA} data, however, will be presented separately.

Results for MAP, cerebral perfusion pressure, $AVDo_2$, $Paco_2$, and HR for both groups are presented in Table 1. There was no significant change in MAP, CPP, $AVDo_2$, $Paco_2$, or HR over the course of the study. However, one patient with a cerebral aneurysm

Table 1. The Effect of Ketamine on Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Arterial-Venous Oxygen Content ($AVDo_2$), $Paco_2$, and Heart Rate (HR)

	Time (min)										
	0	1	2	3	4	5	6	7	8	9	10
MAP (mm Hg)	77 ± 3	77 ± 2	76 ± 3	75 ± 3	75 ± 3	73 ± 3	74 ± 3	75 ± 2	75 ± 2	74 ± 2	75 ± 2
CPP[a] (mm Hg)	63 ± 3	62 ± 2	62 ± 3	62 ± 3	61 ± 3	61 ± 2	61 ± 3	62 ± 2	62 ± 2	61 ± 2	62 ± 2
$AVDo_2$ (vol%)	5.5 ± 0.4					5.7 ± 0.5					5.7 ± 0.5
$Paco_2$ (mm Hg)	34 ± 1					34 ± 1					34 ± 1
HR (bpm)	67 ± 3	66 ± 3	65 ± 3	65 ± 3	65 ± 3	66 ± 3	66 ± 3	66 ± 3	66 ± 3	67 ± 3	66 ± 3

All values are mean ± SE.
Values obtained at $t = 0$ represent baseline measurements obtained prior to the administration of the ketamine.
[a] $n = 17$; all others, $n = 20$.

and one patient with a tumor required phenylephrine to maintain MAP shortly after ketamine administration. Phenylephrine was given in 20-μg increments and the total dose was 60 μg and 80 μg, respectively. These patients were included in the analysis.

The baseline V_{MCA} values for the aneurysm group, the tumor group, and the combined group were 52 ± 7, 36 ± 3, and 44 ± 4 cm/s (mean ± SE), respectively. MCA flow velocity, measured in both absolute values and as percentages of baseline, decreased after ketamine administration (Figure 1). The decrease was significant ($P < 0.0001$) in both groups during the first 7 min of the study. During the last 3 min, V_{MCA} returned to baseline values in the aneurysm group, but remained decreased in the tumor group.

The ICP results are shown in Figure 2. There was a small, but statistically significant ($P < 0.001$), decrease in ICP after ketamine administration. The decrease occurred immediately after the administration of ketamine and continued during the 10-min observation period. There was no correlation between the effect of ketamine and the baseline ICP. This absence of correlation, however, may be due to the small range of ICP values recorded.

There was a significant decrease in total EEG power ($P < 0.02$). Analysis of individual frequency bands revealed that there was a decrease in the absolute values of all the individual bands (data not shown). Despite the decrease in absolute value, as a percent of total power, the β band increased after ketamine administration. All other frequency bands decreased when expressed as a percentage of the total EEG power. Figure 3 illustrates the changes in total EEG power as well as the percent changes of power in the β and δ bands.

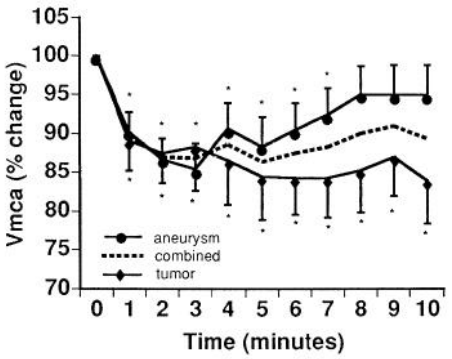

Figure 1. The effect of ketamine on mean cerebral artery blood flow velocity (V_{MCA}). Compared to time 0, values were significant at times 1–7 min for aneurysm patients ($n = 10$), and at all times in the tumor patients ($n = 10$), and the combined group ($n = 20$) ($P < 0.05$). Error bars for the combined group are not shown to improve clarity.

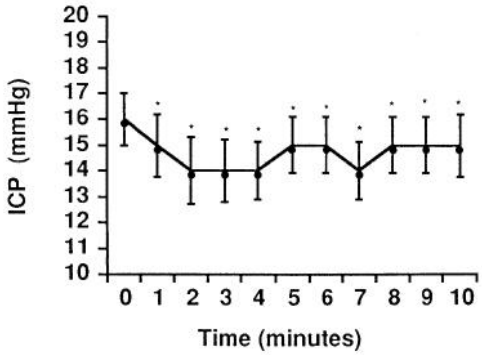

Figure 2. The effect of ketamine on intracranial pressure (ICP). The decrease in ICP was significant ($P < 0.001$) at all times compared to time 0; $n = 17$ patients: 10 aneurysm patients, and 7 tumor patients. All values are mean ± SE.

Discussion

In the present study, we found that ICP was not increased under the study conditions and that the balance between cerebral metabolism and flow was not altered. Depending on the experimental model used, ketamine has been shown to increase (2), decrease (6,10,11), or have no effect (3,4,12) on ICP. This lack of consistency may be due in part to differences in experimental design among studies, such as the absence or presence of other medications or use of background anesthetics, and control of $Paco_2$. For instance, in ventilated neonates, induction of anesthesia with ketamine decreased anterior fontanelle pressure (10), and in ventilated patients with acute head injury, ketamine had no effect on ICP (3).

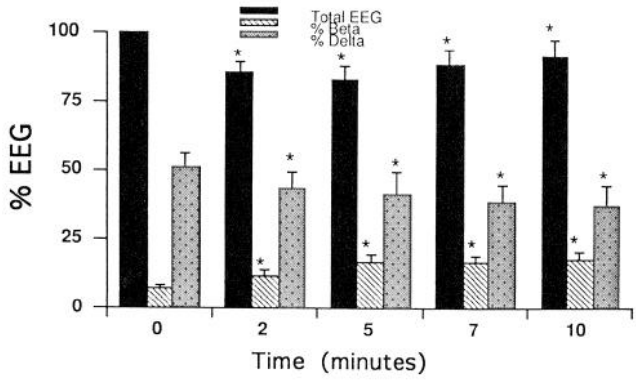

Figure 3. The effect of ketamine on EEG (electroencephalography). There was a significant decrease in the percent of total EEG power ($P < 0.02$). Although there was a decrease in the absolute values of all the individual bands (not shown), the percent β power (% Beta) increased as shown here. There was a percent decrease in all other bands as represented by the δ band ($n = 20$). All values are mean ± SE.

Furthermore, as a NMDA receptor antagonist, ketamine has been shown experimentally to have neuroprotective properties during transient cerebral ischemia (13). However, ketamine is currently considered contraindicated in patients with increased ICP (1). Because there are conflicting results regarding ketamine's effect on cerebral hemodynamics, and ketamine is the only NMDA receptor antagonist currently approved for clinical use as an anesthetic, we believe the use of ketamine in neurosurgical anesthesia warrants a reevaluation.

We found that in anesthetized, ventilated patients, ketamine did not increase ICP or MAP, and that EEG power and V_{MCA} decreased, while $AVDo_2$ did not change. Our results show that during the described study conditions, ketamine does not cause cerebral or systemic stimulation. The metabolic and flow velocity data suggest that ketamine may depress cerebral metabolism and that flow remains coupled to metabolism. Other studies have reported similar effects on ICP (6,10,11), MAP (14), and cerebral hemodynamics (4,15) and metabolism (5,14). However, the cerebral and systemic effects of ketamine are by no means uniform, and extrapolating these findings to other clinical settings should be done with caution. One limitation of our study is that a very specific group of patients was investigated under controlled conditions. None of our patients had severe intracranial hypertension (the highest ICP was 20 mm Hg); they were all anesthetized prior to ketamine administration and were kept normocarbic to mildly hypocarbic. As will be discussed later, all of these factors can alter the effects of ketamine. The relatively homogeneous nature of the study patients may help explain some of our results. However, it should be mentioned that, although the decrease in ICP was small and probably clinically unimportant, this decrease was unrelated to the baseline ICP and was observed in nearly every patient, therefore yielding a significant difference.

We did not directly measure either CBF or cerebral metabolic oxygen consumption ($CMRO_2$). The transcranial Doppler was used because it allows continuous estimation of CBF in a noninvasive fashion. Because V_{MCA} is determined by both CBF and the diameter of the MCA which may vary among the population, absolute values for V_{MCA} and CBF do not correlate well. However, cerebral arterial diameters have been shown to remain fairly constant with changes in blood pressure and CO_2 (16), and the percent change in V_{MCA} has been shown to correlate well with percent change in CBF (17). In the current study, V_{MCA}, in both absolute value and in percentage, decreased after ketamine administration, which is consistent with prior observations assessing the effect of ketamine on CBF during anesthesia (4,17). In both the aneurysm and tumor groups, V_{MCA} decreased after ketamine administration, but the decrease was persistent in the tumor group. The cause of this difference is not readily apparent, but may be related to the lower baseline V_{MCA} in the tumor group. Alternatively, this difference may be more apparent than real; had we extended this observation period beyond 10 min, the V_{MCA} would also return to baseline in the tumor group.

Although $CMRO_2$ was not directly measured, our data suggest that CBF and metabolism remained coupled when ketamine was added to a background anesthetic, because V_{MCA} and total EEG power decreased while $AVDo_2$ remained unchanged. However, since $AVDo_2$ provides a global assessment of the balance between cerebral oxygen supply and demand, it may not reflect regional changes. For instance, Crosby et al. (18) showed that in various parts of the brain, ketamine administered by itself can depress as well as increase cerebral glucose metabolism.

To reconcile our present findings with previously reported effects of ketamine, it is important to discern the contributing roles of modes of ventilation, background anesthetics, and neurologic pathology.

The mode of ventilation appears to have a significant influence on the effect of ketamine. In ventilated neonates, induction of anesthesia with ketamine decreased anterior fontanelle pressure (10). Similarly, Pfenninger and Reith (3) reported that, in ventilated patients with acute head injury, ketamine had no effect on ICP. In contrast, CSFP increases when ketamine is administered to spontaneously breathing patients (2) and may be mediated by an increase in $Paco_2$. In spontaneously breathing rats, ketamine causes an increase in $Paco_2$ and an increase in localized CBF (19). Sari et al. (20) reported that an induction dose of ketamine increased $Paco_2$, CSFP, and CBF in healthy patients. However, if ventilation was altered to produce hypocapnia, then CSFP was

unchanged. These findings are at variance with those reported by Takeshita et al. (21), who found that CBF (and MAP) increased even when ventilation was controlled.

When ketamine is administered with other anesthetics, CBF (4,15) and $CMRO_2$ (14) decrease. Dawson et al. (5) reported that in dogs given thiopental prior to ketamine, $CMRO_2$ decreased modestly and EEG activity changes paralleled alterations in $CMRO_2$. Because the influence of different anesthetics on the systemic and cerebral hemodynamic effect of ketamine is not uniform, our findings may not necessarily be applicable to other types of background anesthetics. During fentanyl and nitrous oxide anesthesia in swine, ketamine decreased CBF and increased $CMRO_2$ and EEG activity in anesthetic doses but not in subanesthetic doses (15). In humans, subanesthetic doses of ketamine without other drugs increased EEG activity and flow velocity (22). When midazolam is administered prior to induction with ketamine, MAP has been shown to either increase (23) or remain unchanged (14). Diazepam (11,24) but not midazolam (11), has been reported to blunt the increase of ICP seen during induction with ketamine, although in one of the studies, ICP increased during tracheal intubation (11).

One possible explanation for our observations is that the neurologic pathology of our patients may have blunted the activation of centrally mediated mechanisms controlling the sympathetic nervous system. Perkins et al. (25) showed, in neurologically injured dogs, that the increases in CBF, ICP, and $CMRO_2$ in response to dizocilpine maleate (MK-801), a NMDA receptor antagonist, were ablated. However, as none of the patients in our study had severe global neurologic injuries, this explanation is unlikely.

A more plausible explanation for our finding is that when ketamine is added to a background anesthetic, its property of central nervous "excitation" is blunted and it increases the "depth of anesthesia." We postulate that with the increase in anesthetic depth, there was a decrease in cerebral metabolic activity, a reduction in CBF and a decrease in cerebral blood volume. The potential decrease in cerebral blood volume could account for the decrease in ICP. The observed decrease in total EEG power supports the possibility that ketamine was acting to increase the "depth of anesthesia." EEG activity (5) and $CMRO_2$ (14) have been shown previously to decrease when ketamine is given in combination with other anesthetics. The contention that the excitatory properties of ketamine are blunted by general anesthesia is supported by the fact that the peripheral vascular stimulation often seen with ketamine was ablated, as demonstrated by a lack of increase in MAP. In fact, two patients required phenylephrine to maintain a normal MAP. The modification or ablation of the increase in MAP associated with ketamine administration has been reported by others (14,26).

In summary, we found that, in ventilated neurosurgical patients with mildly increased ICP and anesthetized with isoflurane and nitrous oxide, ketamine did not increase either MAP or ICP. There was a decrease in V_{MCA} and overall EEG power; the lack of change in $AVDo_2$ suggests the balance between CBF and metabolism was unaffected. The current study does not address any cerebral protective effect of ketamine, nor does it indicate any clinical advantage. Rather, our study shows that ketamine may not be contraindicated in all patients at risk of intracranial hypertension. Our observations demonstrate that ketamine, the only anesthetic currently available for clinical use with NMDA antagonist properties, can be given to ventilated, anesthetized patients without adversely altering cerebral or systemic hemodynamics. Further investigation of the use of ketamine in neurosurgical anesthesia is warranted.

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