

# Safety of sedation with ketamine in severe head injury patients: Comparison with sufentanil

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**Objective:** The aim of the study was to compare the safety concerning cerebral hemodynamics of ketamine and sufentanil used for sedation of severe head injury patients, both drugs being used in combination with midazolam.

**Design:** Prospective, randomized, double-blind study.

**Setting:** Intensive care unit in a trauma center.

**Patients:** Twenty-five patients with severe head injury.

**Interventions:** Twelve patients received sedation with a continuous infusion of ketamine-midazolam and 13 with a continuous infusion of sufentanil-midazolam. All patients were mechanically ventilated with moderate hyperventilation.

**Measurements and Main Results:** Prognostic indicators (age, Glasgow Coma Scale scores, computed tomography diagnosis, and Injury Severity Scale score) were similar in the two groups at study entry. Measurements were carried out during the first 4 days of sedation. The average infusion rates during this time were  $82 \pm 25 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  ketamine and  $1.64 \pm 0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  midazolam in the ketamine group and  $0.008 \pm 0.002 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  sufentanil and  $1.63 \pm 0.37 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  midazolam in the sufentanil group. No significant differences were

observed between the two groups in the mean daily values of intracranial pressure and cerebral perfusion pressure. The numbers of intracranial pressure elevations were similar in both groups. The requirements of neuromuscular blocking agents, propofol, and thiopental were similar. Heart rate values were significantly higher in the ketamine group on therapy days 3 and 4 ( $p < .05$ ). With regard to arterial pressure control, more fluids were given on the first therapy day and there was a trend toward greater use of vasopressors in the sufentanil group. Sedative costs were similar in the two groups.

**Conclusion:** The results of this study suggest that ketamine in combination with midazolam is comparable with a combination of midazolam-sufentanil in maintaining intracranial pressure and cerebral perfusion pressure of severe head injury patients placed under controlled mechanical ventilation. (Crit Care Med 2003; 31:711–717)

**KEY WORDS:** severe head injury management; ketamine; sufentanil; midazolam; sedation; intracranial pressure; cerebral perfusion pressure; adverse effects of anesthetic agents; intensive care unit

The objectives of sedation administered to patients with severe traumatic brain injury are to prevent intracranial hypertension due to pain or agitation and to allow mechanical ventilation. Generally, opioids and benzodiazepines are used. However, both therapies may result in circulatory depression and reduce the cerebral perfusion pressure (CPP) (1–3). In patients with traumatic head injury, CPP has been shown to be a major determinant of outcome (4). Ketamine is an anesthetic drug that combines a potent an-

algesic with hypnotic action; it stimulates the cardiovascular system and may be used during hemorrhagic shock (5). Potential adverse effects of ketamine in neurosurgical anesthesia have been well established (6, 7). However, ketamine has been shown to decrease cerebral blood flow (CBF) and intracranial pressure (ICP) in head trauma, if the patient is under sedation (propofol or midazolam) and  $\text{Paco}_2$  is maintained by controlled mechanical ventilation (8, 9). The potential advantages of using ketamine in sedation of traumatic brain injury patients are maintenance of hemodynamic status as well as CPP, absence of withdrawal symptoms, and better tolerance of enteral nutrition compared with opioids. Furthermore, recently some experiments following traumatic and ischemic brain damage revealed numerous neuroprotective effects of ketamine (10–13).

The purpose of this study was to compare in severe head injury patients the effects of ketamine and sufentanil contin-

uous infusion given in combination with midazolam on ICP control and maintenance of CPP. Patients were studied for the first 4 days of sedation. We evaluated also treatment-related adverse events, quality of recovery, and cost in both sedation groups.

## MATERIAL AND METHODS

**Study Design and Patient Population.** After approval by the ethics committee of our institution and by the institutional review board, informed written consent was obtained from members of the patients' families.

Eligible patients included those age 16–75 yrs who had sustained a traumatic brain injury resulting in a postresuscitation Glasgow Coma Scale (GCS) score (14) of 3–8, who required mechanical ventilation and ICP monitoring because of a postresuscitation GCS score  $\leq 8$ , and for whom computed tomography scan results indicated a significant risk of increased ICP.

Exclusion criteria included life-threatening multiple injuries, kidney or heart insuffi-

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ciency, hepatic failure, body weight of  $\geq 130$  kg, and a history of psychosis.

**Group Assignment and Dosage.** Patients were randomized in a double-blind fashion by using the balanced eight-block sequence generated from a random table, in a 1:1 ratio, to ketamine group or to control (sufentanil) group. The syringes containing the assigned study drug were prepared by the resident druggist so as to provide the dose in a volume of 60 mL, keeping investigators blinded as to whether ketamine or sufentanil was being given. The drugs were diluted to similar volumes that would result in equipotent infusions on a micrograms per kilogram per minute basis: a syringe of 60 mL containing 50 mg of midazolam and 2.5 g of ketamine in the ketamine group and 250  $\mu\text{g}$  of sufentanil in the control group. The sedation was initiated by using a continuous infusion with 1  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  midazolam and 50  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  ketamine or 0.005  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  sufentanil. The rates of syringes were later adjusted as a function of clinical requirements to obtain a quiet patient with ICP values  $< 25$  mm Hg and CPP values  $> 70$  mm Hg.

**Patient Management.** All patients were admitted to the Intensive Care Unit (ICU) after initial stabilization or after craniotomy for evacuation of an intracranial hematoma. They underwent intensive monitoring of GCS score, pupillary response, heart rate (HR), arterial blood oxygen saturation, and end-tidal capnometry. Invasive mean arterial blood pressure (MABP) was continuously monitored via an arterial cannula, and ICP measurements were obtained through a frontal ventricular catheter system with a Camino transducer (Camino V420 monitor, Camino Laboratories, San Diego, CA). From these last two variables, CPP (CPP = MABP - ICP) was continuously calculated and displayed on the monitor. We checked zero level before usage of each Camino transducer.

Management was in concordance with previously published guidelines for managing patients with severe head injury and included an algorithm for maintaining ICP  $< 25$  mm Hg and CPP  $> 70$  mm Hg (15). ICP therapy was implemented in a stepwise fashion as outlined in Table 1. Treatment baseline included mild hyperventilation (Paco<sub>2</sub>, 35  $\pm$  2 mm Hg), normothermia (temperature 37°C), and proci-

tus of 15°. We also collected the following variables, which might have affected ICP and CPP: body temperature, Paco<sub>2</sub>, and arterial hemoglobin oxygen saturation.

**Injury Severity Determinants.** Prognostic indicators were documented, including patient age, postresuscitation GCS score, analysis of first computed tomography scan according to the Traumatic Coma Data Bank (16), and classification and calculation of Injury Severity Scale (ISS) score.

**Efficacy Assessment.** We calculated mean daily ICP and mean daily CPP from 24 values recorded hourly. We noted the total number of times daily that ICP was  $> 25$  mm Hg for  $> 5$  mins and necessitated cerebrospinal fluid drainage.

The infusion rates and the duration of therapy were noted, as was the frequency of use of neuromuscular blocking, propofol, and thiopental. We calculated, during the sedation period, mean daily HR and mean daily MABP from 24 values recorded hourly.

Medications for maintaining blood pressure (volume of fluid replacement or doses of dopamine and norepinephrine) were noted. Tolerance of enteral nutrition was determined by aspiration of gastric residue every morning. Enteral nutrition began on the first day and was increased by 500 mL daily up to 2000 mL per day, if the residue was  $\leq 150$  mL. The rate was reduced by 50% if the residue was  $\geq 250$  mL and was stopped if similar values were found on two consecutive days.

Efficacy of sedation was evaluated during a nociceptive stimulus by using routine intervention during nursing: endotracheal suctioning (17). Twenty-four hours after sedation, the beginning endotracheal suctioning protocol was as follows: baseline monitoring (HR, MABP, ICP, CPP, and mean velocity of middle cerebral artery) of physiologic variables for 5 mins, insertion of standardized suction catheter, application of suction at a flow rate of 16 L/min for 5 secs, monitoring for presence of cough or agitation, and minute by minute postprotocol monitoring of the previously noted variables for a maximum of 10 mins. Cerebral blood flow velocity was measured by using the Waki 2 transcranial Doppler system (Atys Medical, Saint Denis Laval, France).

Efficacy and safety of both treatments were assessed during sedation infusion and 48 hrs after sedation was stopped.

Heart rate, MABP, ICP, and CPP (every 15 mins during the first 3 hrs, then hourly for 8 hrs) assessed the quality of recovery after sedation perfusion stopping. Time to obtain the reactivity (evaluated by GCS score) and requirements for drugs in case of agitation (clonidine, levopromazine, or propofol) were recorded.

We noted the mortality rate due to the intracranial hypertension during the ICU stay. Neurologic outcome was determined at 6 months postinjury by obtaining the Glasgow Outcome Scale score (18).

**Cost Assessment.** Sedative costs were calculated as follows: drugs (ketamine, sufentanil, and midazolam) (\$) + (cost of tubing \$  $\times$  number of intravenous sets) + (number of syringes  $\times$  cost of syringes \$) per patient per day.

**Statistics.** To assess differences for quantitative factors, we used analysis of variance when variances were homogeneous and the Kruskal-Wallis test when variances were heterogeneous. We used chi-square test or Fisher's test to compare qualitative factors. A probability value  $< .05$  was considered significant. Results are presented as their mean  $\pm$  sd.

## RESULTS

**Patient Characteristics and Prognostic Factors.** Twenty-five patients with traumatic brain injury admitted to the trauma ICU met entry criteria: 12 in the ketamine group and 13 in the sufentanil group. Weight was similar between the two groups: 71  $\pm$  9 kg and 68  $\pm$  12 kg. The two groups were homogeneous for predictors of outcome: age, median of postresuscitation GCS score, computed tomography scan, and ISS score (Table 2).

**Trial Drug Administration.** The mean duration of sedation was 6.2  $\pm$  3.2 days in the ketamine group and 5.3  $\pm$  3.8 days in the sufentanil group (nonsignificant).

The average infusion rates on the 4 first days were 82  $\pm$  25  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  ketamine and 1.6  $\pm$  0.5  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  midazolam in the ketamine group, and 0.008  $\pm$  0.002  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  sufentanil and 1.6  $\pm$  0.4  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  midazolam in the other group. Table 3 indicates the increase in midazolam, ketamine, or sufentanil infusion rates in the two groups for patients who still needed sedation.

**ICP, CPP, and Therapy Intensity.** Mean daily ICP and CPP values were similar between the two groups and are shown in Figure 1a and 1b. On the first therapy day, mean daily ICP was 19  $\pm$  8.4 mm Hg in the ketamine group and 15.7  $\pm$  6.8 mm Hg in the sufentanil group (*p*

Table 1. Critical pathway treatment of intracranial hypertension (intracranial pressure  $> 25$  mm Hg)

Step	Therapy
1	Increase sedation if patient is agitated
2	Use intermittent neuromuscular blockade repeatedly if patient remains agitated
3	Ventricular cerebrospinal fluid drainage
4	Osmotherapy (mannitol, 20%; hypertonic saline, 7.5%)
5	Hyperventilation to a Paco <sub>2</sub> of 30 mm Hg and continuous neuromuscular blockade
6	Propofol infusion
7	Monitor Sv̄jO <sub>2</sub> , hyperventilation to a Paco <sub>2</sub> of 25 mm Hg, hypothermia to 32–33°C, and thiopental infusion

Table 2. Characteristics of study patients

	Ketamine (n = 12)	Sufentanil (n = 13)
Age, yrs	30 ± 11	27 ± 7
Sex ratio, M/F	10/2	9/4
Median postresuscitation GCS score	6	5
Median Traumatic Coma Data Bank	3	3
Median ISS	34	29
Mean duration of sedation, days	6.1 ± 3.2	5.3 ± 3.7

GCS, Glasgow Coma Scale; ISS, Injury Severity Scale.

Table 3. Daily dosages of anesthetic drugs in both groups (percentage in relation to initial rate)

	Ketamine Group		Sufentanil Group	
	Midazolam (%) μg/kg/min	Ketamine (%) μg/kg/min	Midazolam (%) μg/kg/min	Sufentanil (%) μg/kg/min
Initial rate	1	50	1	0.005
Day 1	1.4 ± 0.5 (+40)	70 ± 25 (+40)	1.4 ± 0.2 (+40)	0.007 ± 0.001 (+40)
Day 2	1.7 ± 0.5 (+70)	85 ± 23 (+70)	1.7 ± 0.4 (+70)	0.008 ± 0.002 (+60)
Day 3	1.8 ± 0.5 (+80)	88 ± 26 (+76)	1.8 ± 0.3 (+80)	0.009 ± 0.002 (+80)
Day 4	1.9 ± 0.5 (+90)	94 ± 23 (+88)	1.9 ± 0.2 (+90)	0.01 ± 0.001 (+100)

= .28). Similar numbers of ICP elevations were noted in the two groups over the study period (Fig. 1c).

Neuromuscular blocking agents were used by continuous infusion in one patient in the ketamine group and four in the other group ( $p = .18$ ) and by bolus in four patients in the ketamine group and six in the other group. Uncontrollable intracranial hypertension required use of another sedation for four patients in the ketamine group and four in the sufentanil group. Propofol was administered to three patients in the ketamine group and four in the sufentanil group. Thiopental was administered to two and one patient in each group, respectively. During the sedation period, variables that might have affected ICP and CPP (body temperature,  $Paco_2$ , and arterial hemoglobin oxygen saturation) did not differ between the two groups (Table 4).

**Adverse Events.** Figure 2a indicates that patients in the ketamine group had higher HR on therapy day 3 ( $94 \pm 10$  compared with  $78 \pm 18$  beats/min,  $p = .03$ ) and on therapy day 4 ( $101 \pm 12$  compared with  $78 \pm 18$  beats/min,  $p = .01$ ). Mean arterial pressure was similar in the two groups (Fig. 2b).

Volume of fluid administered was significantly less in the ketamine group on therapy day 1 ( $429 \pm 405$  mL compared with  $992 \pm 703$  mL,  $p = .02$ ). There was a trend toward greater use of vasopressors ( $p = .15$ ) in the sufentanil group

(Table 5). Six patients received dopamine in the ketamine group and eight in the sufentanil group (nonsignificant), and norepinephrine was given in seven and 11 patients, respectively (nonsignificant).

Residual gastric volume and tolerance of enteral nutrition were similar in the two groups (Table 6).

**Changes in Systemic and Cerebral Hemodynamics During Endotracheal Suctioning.** Intracranial pressure baseline values (T0) tended to be higher in the ketamine group ( $20.1 \pm 9$  mm Hg) than in the sufentanil group ( $14 \pm 5.2$  mm Hg), but this was not significant ( $p = .07$ ). After endotracheal suctioning, a moderate increase in ICP and a slight decrease in CPP were observed in both groups (Fig. 3). Changes in these variables were not different between the two groups. HR and mean velocity of middle cerebral artery remained unchanged in both groups. The presence of coughing and agitation was not appreciably different in the two groups.

**Recovery Assessment.** Four patients died in the ketamine group and three in the sufentanil group. Thus, awakening was studied in eight patients in the ketamine group and 10 in the sufentanil group.

Changes in ICP, MABP, and HR did not differ significantly between the two groups during the first 8 hrs after perfusion stopped. During this period, because of marked agitation, two patients needed

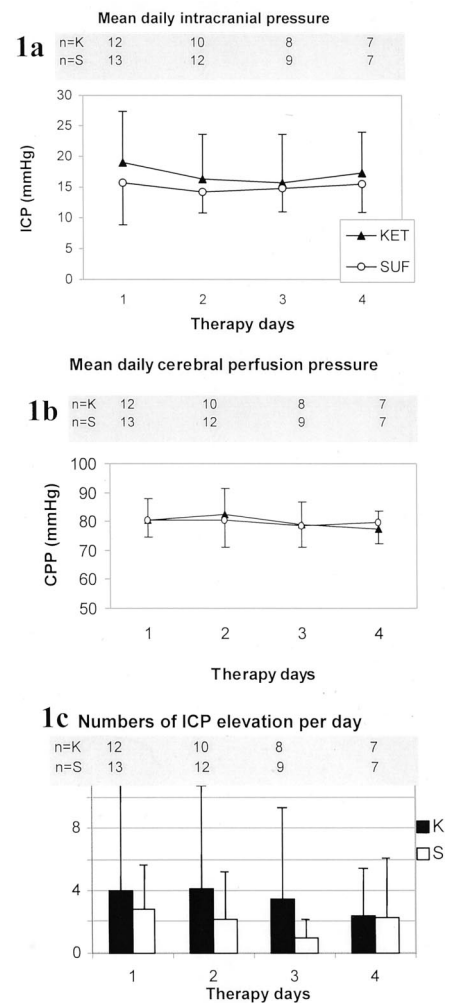


Figure 1. a, Control of intracranial pressure (ICP); b, control of cerebral perfusion pressure (CPP); and c, numbers of ICP elevation (ICP elevation >25 mm Hg and for >5 mins) in the ketamine (KET or K) and sufentanil (SUF or S) groups. No significant difference was observed in mean ICP, CPP values, and numbers of ICP elevation. Over each graphic, n = number of patients in both groups.

clonidine and one levomepronazine in the ketamine group, and two patients needed clonidine and one propofol in the sufentanil group.

Changes in GCS score during the awakening period are presented in Figure 4. After infusion stopped, improvement of GCS score was faster in the sufentanil group ( $p = .01$ ). The GCS score was similar at the patient's recovery between the two groups.

ICU stay was similar in both groups: ketamine group  $21 \pm 13$  days and sufentanil group  $18 \pm 13$  days.

**Mortality Rate and Neurologic Outcome.** During the ICU stay, intracranial hypertension was considered a key factor



Table 4. Variables that might have affected intracranial pressure

	Paco <sub>2</sub>		Body Temperature		Sao <sub>2</sub>	
	Ketamine	Sufentanil	Ketamine	Sufentanil	Ketamine	Sufentanil
Day 1	31 ± 3.8	33 ± 4.5	37.4 ± 1.1	37.6 ± 1	98 ± 1.2	99 ± 1.2
Day 2	32 ± 3.3	33 ± 2.7	36.8 ± 1.8	38 ± 1.1	99 ± 1	98 ± 1.5
Day 3	34 ± 2.4	34 ± 3.1	37.6 ± 1.2	37.5 ± 1.6	97 ± 1.7	99 ± 0.8
Day 4	36 ± 3.6	34 ± 2.5	37.6 ± 1.5	37.4 ± 1.8	97 ± 1.5	98 ± 1.5

Sao<sub>2</sub>, arterial oxygen saturation.

for death in four patients in the ketamine group and three in the sufentanil group. At 6 months postinjury, a favorable outcome, as assessed by the Glasgow Outcome Scale score, was observed in four of the ketamine group patients and in six of the sufentanil group patients. Two death were noted in ketamine group and one in sufentanil group.

**Sedation Cost.** The mean daily cost was 47 ± 13 U.S. dollars for ketamine-midazolam combination and 42 ± 14 U.S. dollars for sufentanil-midazolam combination per day and per patient. When we included propofol and thiopental charges, mean daily cost was 67 ± 53 in the ketamine group and 51 ± 29 U.S. dollars in the sufentanil group (nonsignificant).

## DISCUSSION

Ketamine is a noncompetitive N-methyl-D-aspartate receptor antagonist with the thalamocortical projection system as the primary site of action. It is usually avoided in the anesthetic management of patients at risk for intracranial hypertension because early studies demonstrated increases in cerebral metabolic oxygen consumption, CBF, and ICP (6, 7).

In fact, these results are controversial. Because of the diversity in experimental design among studies and the multiple factors that appear to influence cerebral hemodynamics, the pharmacologic action of ketamine remains poorly known. The cerebrovascular effects of ketamine are related to the preexisting cerebrovascular tone induced by background anesthetic (19, 20). So, the increase in Paco<sub>2</sub> levels subsequent to ketamine application to spontaneously breathing patients is responsible for an increase in either CBF or ICP (7). Impairment of CBF autoregulation and dose of ketamine used play a role (21). Ketamine inhibits some brain areas but at the same time stimulates some others, so it leads to a decrease in CBF

and cerebral metabolic oxygen consumption in some areas and to an increase in others (22). Anesthetic drugs such as ketamine or midazolam modulate CBF and consequently their own transport rate to the brain (23). Midazolam suppresses the cardiostimulation of ketamine and then the increase in ICP (9). For others, it antagonizes the excitatory cerebral effects associated with an increased cerebral metabolic oxygen consumption (20, 24).

Recent studies on the use of ketamine reported no increase in ICP when ventilation was controlled (25–27) or when midazolam was given concurrently (9, 20).

The advantages of ketamine administration compared with opioids should be the maintenance of the hemodynamic status and a better CPP control, a better tolerance of enteral nutrition, and absence of withdrawal symptoms.

In the present study we showed that, under conditions of controlled ventilation and in combination with midazolam, the use of ketamine leads to the same ICP levels as sufentanil. These findings are in agreement with our previous study in which not only was no increase in ICP observed, but a significant pressure reduction occurred after the three doses of ketamine (1.5, 3, and 5 mg/kg) in mechanically ventilated head-trauma patients sedated with propofol (8). Kolenda et al. (28) reported slightly higher ICP values (2 mm Hg) in head injury patients sedated with ketamine compared with those sedated with fentanyl. But, due to the positive effect of ketamine on blood pressure, they documented a higher value of CPP (about 8 mm Hg) than in the fentanyl group. We found no significant differences between CPP values in both groups over our study period.

In our trial design, one group of patients were sedated with sufentanil-midazolam. This may be of concern since sufentanil has been demonstrated to in-

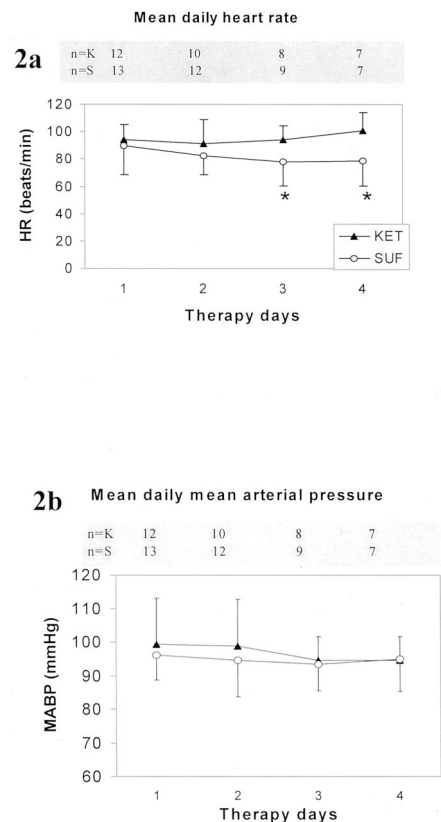


Figure 2. Systemic hemodynamics in patients sedated with ketamine or sufentanil. Heart rate (HR) increased on therapy day 3 ( $p = .03$ ) and day 4 ( $p = .01$ ) in ketamine group. No significant changes in mean arterial blood pressure (MABP) were observed. \* $p < .05$ .

crease ICP in patients with decreased intracerebral compliance (29). This deleterious effect was observed when the drug was given by bolus injection. The increase in ICP can be blunted by maintaining mean arterial pressure using norepinephrine infusion (30). When sufentanil is given by continuous infusion, such an ICP increase is no longer observed. Therefore, it is wise to avoid using opioids by bolus injections in head trauma patients. In the present study, sufentanil was administered by continuous infusion, as was ketamine.

The requirements regarding neuromuscular blocking agents, propofol or thiopental, and the number of dosage adjustments were similar in the two groups. The average infusion rate (82  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) for ketamine was comparable to that used by others (28). The sedation infusion rates had to be increased in both groups to maintain the same level of sedation, and this was related to tachyphylaxia and pharmacokinetics factors.

Table 5. Hemodynamic treatments in both groups

	Fluid Dosage, mL		Dopamine Dosage, $\mu\text{g}/\text{kg}/\text{min}$		Norepinephrine Dosage, $\mu\text{g}/\text{kg}/\text{min}$	
	Ketamine	Sufentanil	Ketamine	Sufentanil	Ketamine	Sufentanil
Day 1	429 $\pm$ 405	992 $\pm$ 703 <sup>a</sup>	4.8 $\pm$ 6.0	8.3 $\pm$ 7.7	0.28 $\pm$ 0.32	0.48 $\pm$ 0.55
Day 2	363 $\pm$ 308	500 $\pm$ 674	4 $\pm$ 6.1	6.9 $\pm$ 7.5	0.2 $\pm$ 0.25	0.68 $\pm$ 0.87
Day 3	350 $\pm$ 474	327 $\pm$ 343	3.8 $\pm$ 7.2	7 $\pm$ 8.4	0.22 $\pm$ 0.27	0.34 $\pm$ 0.47
Day 4	114 $\pm$ 203	71 $\pm$ 188	2 $\pm$ 5.2	6 $\pm$ 7.5	0.14 $\pm$ 0.16	0.37 $\pm$ 0.51

<sup>a</sup>*p* < .05.

Table 6. Tolerance of enteral nutrition

	Patients with Enteral Nutrition		Residual Gastric Volume, mL	
	Ketamine	Sufentanil	Ketamine	Sufentanil
Day 1	9/12	9/13	154 $\pm$ 282	107 $\pm$ 101
Day 2	10/10	11/12	281 $\pm$ 421	83 $\pm$ 148
Day 3	8/8	8/9	290 $\pm$ 615	72 $\pm$ 210
Day 4	7/7	7/7	78 $\pm$ 152	128 $\pm$ 262

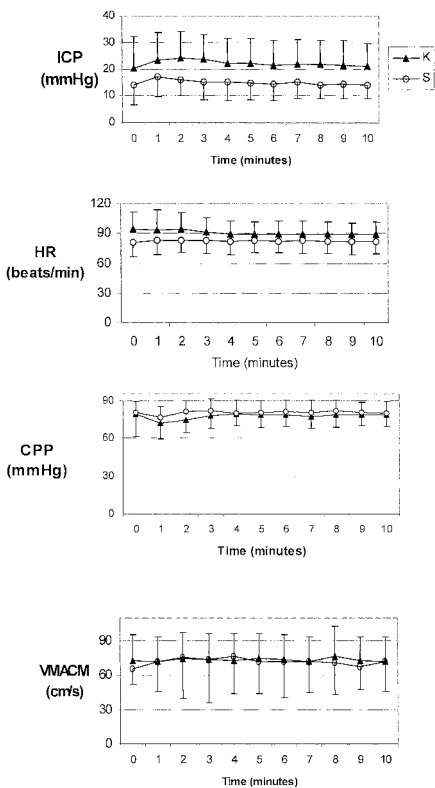


Figure 3. Evolution of intracranial pressure (ICP), cerebral perfusion pressure (CPP), heart rate (HR), and mean velocity of middle cerebral artery ( $V_{MACM}$ ) during endotracheal suctioning in the ketamine (K) and sufentanil (S) groups. Baseline monitoring is represented by T0.

HR was significantly higher on therapy days 3 and 4 in the ketamine group. Although MABP values were similar in

the two groups, fluid requirement was greater on the first therapy day and there was a trend toward a greater use of vaso-pressors in the sufentanil group. This can probably be related to the cardiostimulation properties of ketamine (31).

Intolerance to gastric nutrition is not uncommon in sedated patients and is associated with a higher mortality rate for the same severity of illness (32). Opioids are acknowledged to reduce the rate of gastric emptying (33). In this study we found the same tolerance to enteral nutrition in the two groups. Other authors who compared gastric emptying in brain-injured patients sedated with either an opioid-based regimen or propofol reported the same results (34).

Transient intracranial hypertension in patients with traumatic brain injury frequently occurs in response to noxious stimuli, such as endotracheal suctioning (35). Several treatments are used to prevent these ICP elevations (opioids or neuromuscular blocker bolus injection, hyperventilation, or intratracheal lidocaine administration), but none of them have proven efficacy. We evaluated sedation efficacy in both groups during endotracheal suctioning and found no significant difference between the two groups with regard to ICP or CPP changes.

We noted a longer recovery time in the ketamine group after the infusion was stopped. Two studies that compared ketamine with fentanyl reported opposite results (28, 36). A similar observation was made in pediatric patients in whom mi-

dazolam or ketamine was administered for sedation for minor laceration repair (37). Patients who received ketamine remained in the emergency department longer than those receiving midazolam or no sedation, but this was considered as only a moderate increase in time by the authors. Ketamine possesses a metabolite, norketamine, that has some hypnotic effects. Probably ketamine or its metabolite has a longer elimination half-life than sufentanil after several days of treatment. This is a disadvantage for sedation in patients with severe brain injury if a rapid recovery is needed for neurologic evaluation. However, this delay was observed after a mean of 6 days of sedation, and further studies should investigate whether such a delay is observed after 24 or 48 hrs of ketamine use.

Sedation cost calculated per person and per therapy day was similar in the two groups: 47  $\pm$  13 U.S. dollars per patient for ketamine-midazolam combination and 42  $\pm$  14 U.S. dollars for sufentanil-midazolam combination.

Preparation of ketamine-midazolam syringes requires ten vials of ketamine and that of sufentanil-midazolam one vial of sufentanil. Thus, the time to prepare ketamine-midazolam seems to be shorter than that required to prepare sufentanil-midazolam. But practical experience shows that use of sufentanil following narcotics legislation is more arduous and requires more time for medical staff.

Our study has some limitations. Indeed there are some disturbing although

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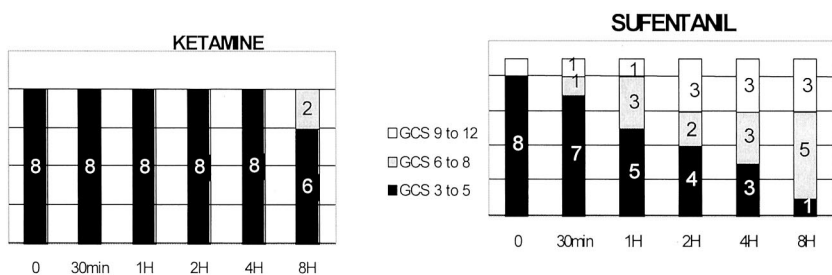


Figure 4. Graphics show changes in Glasgow Coma Scale (GCS) score after infusion stopped in the ketamine and the sufentanil group (numbers in the columns stand for the actual number of patients). Elevation of GCS was more rapid in the sufentanil group. \* $p < .05$ .

nonstatistically significant trends in the study patients. On day one, ICP was slightly higher in the ketamine group ( $p = .28$ ); favorable outcome, as judged by the Glasgow Outcome Scale at 6 months, was more common with sufentanil group ( $p = .99$ ); and ICU stay was longer in the ketamine group ( $p = .64$ ). Whether these nonsignificant trends can translate into clinically significant concerns is unknown. This should be carefully evaluated with a larger number of patients. Because of the design of the study, it suffers from a lack of power: Indeed, to have a type I error of 5% and a type II error of 10% (i.e., a power of 90%), >100 patients should be included in each group. At the present stage, our preliminary data indicate that the combination ketamine-midazolam favorably compares with sufentanil-midazolam, but the concerns regarding the aforesaid variables should be clarified by studying larger groups of patients.

In summary, this study strongly suggests that the continuous infusion of ketamine-midazolam is as efficient as that of sufentanil-midazolam on ICP and CPP control in patients with severe head injury. We noted significantly lower fluid requirement and a trend toward lesser use of vasopressors with ketamine administration to obtain similar MABP values. We observed a similar tolerance of enteral nutrition in the two groups. Recovery was slower with ketamine than sufentanil, but this did not affect the ICU length of stay.

Thus, ketamine could be considered for prolonged sedation in patients with head injury under controlled conditions and in combination with midazolam. However, further studies with larger groups of patients should be undertaken before recommending routine use of combination ketamine-midazolam in patients with traumatic brain injury.

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