Ketamine Sedation in Traumatic Brain Injury: Friend or Foe?

G. Christina Caballero, Pharm.D.

PGY2 Critical Care Pharmacy Resident
Department of Pharmacy, University Health System, San Antonio, TX
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center,
University of Texas Health Sciences Center at San Antonio

September 16, 2011

Learning Objectives:
1. Describe intracranial physiology and the relationship between mean arterial, cerebral perfusion, and intracranial pressures
2. List the goals to preserve brain function in traumatically brain injured patients
3. Outline treatment strategies for elevated intracranial pressure
4. Differentiate ketamine from other available sedatives
5. Evaluate evidence regarding ketamine use in traumatically brain injured patients
I. Traumatic Brain Injury (TBI)
   a. Major cause of disability and death
   b. 1.5 million TBIs occur in the U.S. each year
   c. Neurologic damage after TBI related to secondary injury and evolves over hours to days following injury
   d. Improved outcomes result when these secondary, delayed insults are prevented
   e. Classification of TBI based on Glasgow Coma Scale Score (GCS) (Appendix A)
      i. Mild: 13-15
      ii. Moderate: 9-12
      iii. Severe: 3-8

II. Intracranial Physiology
   a. Contents
      i. Skull provides a rigid enclosure for brain with fixed volume of 1400-1700 mL
      ii. Contents under physiologic conditions
         1. Brain parenchyma (80%)
         2. Blood (10%)
         3. Cerebral spinal fluid (CSF) (10%)
            a. Normally produced at 20 mL/hr and reabsorbed by venous system
            b. Dysregulation can occur in situations of impaired outflow
   b. Autoregulation
      i. Cerebral blood flow (CBF) maintained constant across mean arterial pressure (MAP) 50-150 mmHg and cerebral perfusion pressure (CPP) 50-100 mmHg
      ii. Cerebral compensatory mechanisms
         1. Triggered by changes in blood pressure and cerebral CO₂ and O₂
         2. Increase in one component compensated for by decrease in volume of another component, increase in intracranial pressure (ICP) or both (Figure 1)
         3. Increases in cerebral volume compensated by
            a. Displacement of CSF into thecal sac
            b. Venous volume decrease via constriction and extracranial drainage
         4. When compensatory mechanisms are dysfunctional or have been exhausted small increases in volume lead to large increases in ICP
         5. Disrupted in about 1/3 of patients with severe TBI
      iii. CPP = MAP – ICP

Figure 1.
III. **Brain Trauma Foundation**¹
   a. Evidence-based guidelines for management of TBI patients
   b. Guidelines in collaboration with American Association of Neurologic Surgeons and Congress of Neurologic Surgeons

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Physiologic Basis</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Perfusion Pressure</td>
<td>Measure of blood supply to brain</td>
<td>CPP 60-70 mmHg</td>
</tr>
<tr>
<td></td>
<td>Ischemia: &lt; 60 mmHg</td>
<td></td>
</tr>
<tr>
<td>Intracranial Pressure</td>
<td>Increased ICP leads to decreased CPP</td>
<td>ICP &lt; 20 mmHg</td>
</tr>
<tr>
<td>Mean Arterial Pressure</td>
<td>CPP is a function of MAP and ICP</td>
<td>MAP &gt; 70 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systolic blood pressure &gt; 90 mmHg</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>The brain requires oxygen for glucose utilization</td>
<td>SaO₂ ≥ 90%</td>
</tr>
<tr>
<td>Sedation and Analgesia</td>
<td>Reduce metabolic demand and response to painful or noxious stimuli</td>
<td>Pain rating scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ramsay Sedation Scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart rate (HR), blood pressure, and respiratory rate</td>
</tr>
<tr>
<td>Seizure Prophylaxis</td>
<td>Seizure activity increases CBF and metabolic demand increasing ICP</td>
<td>Seizure prophylaxis for 7 days</td>
</tr>
<tr>
<td>Volume Status</td>
<td>CPP and MAP are maintained as a function of cardiac output</td>
<td>CVP 8-15 mmHg for mechanical ventilated patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR and MAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine output &gt; 0.5 mL/kg/hr</td>
</tr>
<tr>
<td>Electrolyte Balance</td>
<td>Electrolytes are used for numerous aspects of maintaining MAP and metabolism</td>
<td>All electrolytes within normal physiologic limits</td>
</tr>
<tr>
<td>Glycemic Control</td>
<td>Hyperglycemia may aggravate ischemic brain injury</td>
<td>Glucose 140-180 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia decreases glucose delivery to brain</td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>TBI patients may have higher metabolic needs and nitrogen wasting</td>
<td>Caloric goal: 30-50 kcal/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20% of feeding should be protein</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Begin within 72 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feed to caloric goal within 7 days</td>
</tr>
</tbody>
</table>
IV. **Intracranial Pressure**\(^1,^3,^15\)

a. Elevated ICP decreases cerebral perfusion and therefore cerebral oxygen and glucose delivery
   i. Associated with increased mortality and worse neurologic outcomes
   ii. Intervention shown to improve outcomes

b. Signs of elevated ICP
   i. Headache, nausea, vomiting, somnolence, pupillary dilation

c. Monitoring ICP provides an early indicator of worsening neurologic pathology and tool to guide management

d. Indications for ICP monitoring
   i. GCS ≤ 8
   ii. Computerized tomography (CT) scan showing evidence of mass effect lesions such as hematomas, contusions, or swelling

e. Relative indications for ICP monitoring
   i. Severe TBI with normal CT scan and two or more of following features:
      1. Age > 40 years
      2. Unilateral or bilateral motor posturing
      3. SBP < 90 mmHg

V. **Treatment of Elevated ICPs**\(^1,^15-^17\)

a. Generally indicated for sustained ICP > 20 mmHg

b. Non-Pharmacologic treatment options for elevated ICP
   i. Surgical\(^1^8\)
      1. Extraventricular Drainage (EVD)
         a. Goal: CSF removal at rate of 1-2 mL/min for 2-3 minutes until ICP < 20 mmHg or CSF no longer obtained
      2. Decompression to remove intracranial space-occupying lesion
   ii. Hyperventilation-induced vasoconstriction\(^20-^23\)
      1. \(\text{CO}_2\) causes cerebral vasodilation and has linear relationship with CBF
      2. Not recommended in initial 24 hours
      3. Prophylactic use not recommended
   iii. Therapeutic Hypothermia\(^24-^27\)
      1. May provide neuroprotection and prevent secondary injury
      2. Routine use is not recommended

c. Pharmacologic treatment options for elevated ICP\(^28-^30\)
   i. Osmotic Therapy
      1. Mannitol
         a. Immediate ICP reduction due to plasma expansion
         b. Osmotic effect after 15-30 minutes once gradients are established between cells and plasma
         c. Dose: 0.25-1 g/kg IV
         d. Monitor: serum osmolality, volume status, chemistry
      2. Hypertonic Saline
         a. Mobilization of water across the blood-brain barrier which reduces cerebral water content and pressure
         b. Concentrations: 2%, 3%, 5%, 7.5%, and 23.4%
c. Dose: bolus or continuous infusion
   d. Monitor: serum sodium and serum osmolarity

3. Hypertonic saline may result in better outcomes and control of ICP

   ii. Pentobarbital
      1. Acts at GABA receptor to reduce brain metabolism and CBF thus lowering ICP and possibly exerting a neuroprotective effect
      2. Indicated for intracranial hypertension refractory to conventional therapy
      3. Onset is immediate, with variable duration of action, and T½ of 19 hrs
      4. Monitor: level (30-40 mcg/mL) and electroencephalogram (EEG)

   iii. Alternative therapies
      1. Sedatives
      2. Analgesics
      3. Antihypertensives
      4. Vasopressors

<table>
<thead>
<tr>
<th>Sedative Agents</th>
<th>Mechanism of Action</th>
<th>Dose and Pharmacokinetics</th>
<th>Effect on MAP, CPP, ICP</th>
</tr>
</thead>
</table>
| Benzodiazepine  | Enhance inhibitory effect of GABA on neuronal excitability by increasing neuronal membrane permeability to chloride, causing membrane hyperpolarization | Midazolam: Dose 0.02-0.1 mg/kg/hr
Onset: 1-2 min
Duration: 30-80 min
T½: 2-6 hrs
Lorazepam: Dose: 0.01 to 0.1 mg/kg/hr
Onset: 10-15 min
Duration: 6-8 hrs
T½: 12 hrs | MAP: ↓
CPP: ↓
ICP: ↑ or ↔ |
| Propofol        | Thought to be GABA agonist, N-methyl-D-aspartate (NMDA) and Ca²⁺ channel antagonist | Dose: 5-75 mcg/kg/min
Onset: 1-2 min
Duration: 3-10 min
T½: 1.5-12 hrs | MAP: ↓
CPP: ↓
ICP: ↓ |
| Dexmedetomidine | Relatively selective alpha-2 adrenergic agonist                                      | Dose: 0.1-1 mcg/kg/hr
Onset: 5-10 min
Duration: 60-120 min
T½: 2 hours | MAP: ↓
CPP: UKN
ICP: UKN |
| Ketamine        | Binds NMDA receptors in the central nervous system, interactions with opiate receptors at central and spinal sites, and interaction with norepinephrine, serotonin, and muscarinic cholinergic receptors | Dose: 0.01-0.03 mg/kg/min or 0.6-1.8 mg/kg/hr
Onset: 30-40 sec
Duration: 5-10 min
T½: 2-3 hrs | MAP: ↑
CPP: ?
ICP: ? |
Management of Elevated Intracranial Pressure\textsuperscript{1,15-17}

Evidence of elevated ICP based on GCS, CT scan, and clinical signs

\textbf{Initial Management}
- O\textsubscript{2} saturation > 90\% or PaO\textsubscript{2} > 60 mmHg
- SBP > 90 mmHg
- Head elevation at 30° and midline position
- Sedation and analgesia
- Seizure prophylaxis

\textbf{Surgical Intervention}
- EVD with or without decompression

\textbf{ICP} > 20 mmHg

\textbf{Nonpharmacologic Treatment}

\textbf{ICP} > 20 mmHg

- Monitor chemistry every 4-6 hours
- Repeat as necessary

- Hypertonic Saline
- Mannitol

\textbf{ICP} > 20 mmHg

- May repeat if serum osmolarity < 320 mOsmol/L and patient is euvoletic

\textbf{Alternative Therapy}

\textbf{Pentobarbital}

\textbf{Reassess Nonpharmacologic Therapy}
VI. Ketamine

a. Mechanism of Action
   i. Noncompetitive inhibition of glutamate activation via NMDA channel

b. Formulations
   i. Ketamine exists as 2 optical isomers or enantiomers, S(+) ketamine hydrochloride and R(-) ketamine hydrochloride
   ii. S(+) enantiomer exhibits more potent anesthetic/analgesic activity with a lower propensity for emergence reactions and agitated behavior
   iii. Commercial preparations only available as racemic mixture of the S(+) and R(-) enantiomers in equal amounts

c. Pros
   i. Sedation
      1. Produces cataleptic state in which patient is completely unaware of the environment
   ii. Analgesia
      1. May be due to multiple mechanisms
         a. Blocks afferent signals associated with the affective-emotional components of pain perception without significantly impairing conduction of signals related to localization of somatic stimuli
         b. NMDA receptor is involved in pain perception
            i. Inhibits nitric oxide (NO) synthesis via NO synthase
               1. NO is a neurotransmitter involved in pain perception centrally and peripherally
      2. Analgesia outlasts anesthesia and occurs at subanesthetic doses
   iii. Cardiovascular Effects
      1. Induces inhibition of neuronal reuptake of catecholamines
      2. Dose-related increase in heart rate, blood pressure and cardiac output
      3. Lower requirement for vasopressor support
   iv. Pulmonary Effects
      1. Causes bronchodilation via increase in catecholamine activity at beta 2 and inhibition of vagal pathways producing anticholinergic effects

d. Cons
   i. Emergence reactions
      1. Characterized by floating sensations, vivid dreams, blurred vision, hallucinations, and delirium
      2. Thought to be due to depression of auditory and visual relay nuclei causing misinterpretation and misperception of auditory and visual stimuli
      3. Decreased incidence and severity with use of midazolam
   ii. ICP and CPP
      1. Early trials found increase ICP and CPP in TBI patients
VII. Ketamine Controversy - Data from the 1970s

a. Takeshita et al\textsuperscript{33} - 1972
i. Evaluated ketamine effects in 10 healthy patients scheduled for elective operations
ii. Ketamine 2 mg/kg IV followed by ketamine 1 mg/kg five minutes later
iii. Respiration was assisted to maintain normocarbia
iv. Results and interpretation
   1. Ketamine increased CPP, PaCO\textsubscript{2}, and jugular venous PO\textsubscript{2}, decreased cerebral vascular resistance (CVR), with no effect on cerebral metabolism
   2. The authors contest that the rise in CBF was too great to be a result of the rise in CO\textsubscript{2} only and that the ketamine must be responsible
      a. This argument is justified however, elevated CBF alone is not harmful
   3. From the MAP and CPP values provided ICPs increased following ketamine administration but remained < 20 mmHg

b. Gibbs\textsuperscript{34} - 1972
i. Evaluated ketamine effects on CSF pressures in healthy patients (n=11) and with space occupying lesions (n=9)
ii. Ketamine 1-1.3 mg/kg IV once
iii. All patients mechanically ventilated
iv. Results and interpretation
   1. Lumbar CSF pressures and MAPs rose in patients with intracranial lesions and were unaffected in healthy patients
   2. All blood gas levels were within normal limits
   3. CSF pressures increased in patients with intracranial lesions, however without ICP or CPP data this is difficult to apply clinically

c. Gardner et al\textsuperscript{35} - 1971
i. Evaluated ketamine effect on CSF pressure in 11 healthy male volunteers undergoing routine surgical procedures
ii. Ketamine 2 mg/kg IV once
iii. Results and interpretation
   1. CSF pressures, MAP, and PaCO\textsubscript{2} increased from baseline
   2. CSF pressures increased following ketamine however these values may transiently rise prior to compensation and ICPs were not mentioned
   3. Increase in CO\textsubscript{2} is difficult to interpret because patients allowed to breath spontaneously and may simply reflect relaxation following ketamine

d. Hershey\textsuperscript{36} - 1972
i. 17 year old with intracranial abnormalities admitted for unrelated procedure
ii. Ketamine 2 mg/kg IV once
iii. Results and interpretation
   1. ICP remained constant, while slight increases in MAPs were seen

e. Gardner\textsuperscript{37} - 1972
i. 34 year old man with intracranial abnormality admitted for related procedure
ii. Ketamine 2 mg/kg IV once
iii. Results and interpretation
   1. Intracranial CSF pressure rose after injection and peaked at < 20 mmHg
   2. Intracranial CSF pressure increased but not to a clinically significant level
3. In the absence of reported blood gas variable it is impossible to say this is due to ketamine alone

VIII. Revisiting an Old Friend – Data from the 1990s
   a. Albanese et al\textsuperscript{38} – 1997
      i. Prospective randomized trial of effects of ketamine on cerebral hemodynamics and EEG activity in 8 patients with TBI
      ii. Ketamine 1.5 mg/kg, 3 mg/kg, 5 mg/kg IV at 6 hour intervals
      iii. All patients received propofol and sedation level was deepened with each ketamine dose increase
      iv. PaCO\textsubscript{2} maintained at 35-38 mmHg
      v. Results and interpretation
         1. Statistically significant increases in ICP were seen at single time points
         2. No statistically significant differences were seen in MAP or CPP
         3. Ketamine was associated with increased ICPs however these values never reached clinical significance ( > 20 mmHg)
         4. Due to coadministration of propofol is it impossible to attribute study findings to ketamine alone
   b. Kolenda et al\textsuperscript{39} – 1996
      i. Prospective, randomized trial of 24 patients with moderate or severe head injury
      ii. Treatment arms – midazolam 6.5 mg/kg/day (0.27 mg/kg/hr) plus
         1. Ketamine 65 mg/kg/day (2.7 mg/kg/hr) or
         2. Fentanyl 65 mcg/kg/day (2.7 mcg/kg/hr)
      iii. Results and interpretation
         1. ICP was generally higher in ketamine group and reached statistical significance on days 8 and 10
         2. Days with ICP > 20 mmHg was 19 for ketamine patients versus 12 days for fentanyl patients
         3. Six-month Glasgow Outcome Scale Score (GOS), therapy failure, and death similar between groups
         4. Ketamine was associated with higher ICPs throughout the 14 day study period, though mean ICPs were always < 20 mmHg
IX. What We Know About Ketamine Now – Data from the 2000s

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
<tr>
<td><strong>Design</strong></td>
</tr>
</tbody>
</table>
| **Population** | ● Inclusion  
  ○ Age 18 years or older with severe TBI defined as: post-resuscitation GCS <9, analysis of the first CT scan according to the Traumatic Coma Data Bank ≥2 (Appendix D), ICP monitoring requirement  
  ● Patients were randomized according to randomization table  
  ○ Ketamine and midazolam (n=15)  
  ○ Sufentanil and midazolam (n=15) |
| **Methods** | ● Target-controlled infusion (TCI) was started when intracranial monitoring was required  
  ○ TCI initial targets  
    ● Ketamine: 1.0 mcg/mL  
    ● Sufentanil: 0.3 ng/mL  
    ● Midazolam: 100 ng/mL  
  ○ Twenty-four hours after the onset of sedation target plasma concentrations were doubled  
  ○ Arterial drug concentrations taken 5 minutes before and 15 minutes after concentration change  
  ● Efficacy of sedation evaluated by five criteria based on behavioral pain scale  
  ○ Absence of agitation; no fighting with ventilator; relaxed facial expression; absence of tachycardia, hyperventilation, and hypertension; absence of intracranial hypertension related to nociceptive stimulations (external noises, lights on/off, interventions on intravascular catheters)  
  ● PaCO₂ maintained between 35 and 38 mmHg  
  ● MAP, ICP and CPP as well as mean velocity of middle cerebral artery (V₉₅₆) were monitored continuously  
  ● EEG was recorded continuously and reported bispectral index (BIS) |
| **Statistics** | ● Data presented as mean ± SD  
  ● Baseline values represent an average of 5 measurements obtained during 5 minute period before increase  
  ● Qualitative data were compared using chi-square test  
  ● Quantitative data were compared using Student’s t-test  
  ● Physiologic measures were analyzed with repeated-measures analysis of variance and the Newman-Keuls’ test  
  ● Statistical significance set at p < 0.05 |
### Results

<table>
<thead>
<tr>
<th>Baseline Measurements</th>
<th>Ketamine (n=15)</th>
<th>Sufentanil (n=15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP</td>
<td>16.2 ± 6.4 mmHg</td>
<td>17.7 ± 6.5 mmHg</td>
<td>NS</td>
</tr>
<tr>
<td>CPP</td>
<td>85 ± 14 mmHg</td>
<td>80 ± 14 mmHg</td>
<td>NS</td>
</tr>
<tr>
<td>$V_{MCAM}$</td>
<td>60 ± 33 cm/sec</td>
<td>77 ± 21 cm/sec</td>
<td>0.03</td>
</tr>
<tr>
<td>BIS</td>
<td>74 ± 20%</td>
<td>65 ± 25%</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD unless otherwise specified

- No statistically significant differences were seen in baseline ICP, CPP, or BIS between groups
- Baseline $V_{MCAM}$ was statistically higher in the sufentanil group
- No difference in ICP, CPP, or $V_{MCAM}$ after the two-fold increase in plasma concentration
- A significant difference occurred 6, 7, and 13 minutes in BIS ($p < 0.05$)

<table>
<thead>
<tr>
<th></th>
<th>Ketamine (mcg/mL)</th>
<th>Sufentanil (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measured concentration</strong></td>
<td>Before Increase</td>
<td>After Increase</td>
</tr>
<tr>
<td>Ketamine</td>
<td>2.6 ± 2.2</td>
<td>5.5 ± 3.8</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.4 ± 0.2</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td><strong>Predictive concentration</strong></td>
<td>Before Increase</td>
<td>After Increase</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1.6 ± 0.8</td>
<td>3.2 ± 1.6</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.4 ± 0.1</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td><strong>Measured midazolam concentration</strong></td>
<td>Before Increase</td>
<td>After Increase</td>
</tr>
<tr>
<td>Ketamine</td>
<td>232 ± 149</td>
<td>228 ± 143</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>284 ± 246</td>
<td>278 ± 241</td>
</tr>
<tr>
<td><strong>Predictive midazolam concentration</strong></td>
<td>Before Increase</td>
<td>After Increase</td>
</tr>
<tr>
<td>Ketamine</td>
<td>138 ± 60</td>
<td>138 ± 60</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>158 ± 75</td>
<td>158 ± 75</td>
</tr>
</tbody>
</table>

- At predicted plasma concentrations, the five criteria for efficacy of sedation were obtained for all patients
- Infusion rates:
  - Ketamine arm
    - Ketamine: 95 mcg/kg/min (5.7 mg/kg/hr)
    - Midazolam: 1.5 mcg/kg/min (0.09 mg/kg/hr)
  - Sufentanil arm
    - Sufentanil: 0.007 mcg/kg/min (0.42 mcg/kg/hr)
    - Midazolam: 1.7 mcg/kg/min (0.1 mg/kg/hr)

### Conclusions

Two-fold increase in sufentanil or ketamine plasma concentration by TCI does not cause changes in ICP or CPP in patients with TBI

### Strengths

- Prospective, randomized trial
- All patients had ICP and CPP monitoring

### Limitations

- Small patient population
- Short study period does not reflect effects of multiple days of therapy
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Statistics</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
**Results**

- Ketamine (n=12) and fentanyl (n=12) arms were similar at baseline
- GCS was lower in the ketamine arm 7.8 ± 4.6 compared to 9.4 ± for fentanyl
- ICP and CPP
  - No statistical difference seen in ICP or CPP between groups
  - Medical management for ICP > 20 mmHg with 20% mannitol or 2 mL/kg 7.5% hypertonic saline
    - Ketamine: 8 patients
    - Fentanyl: 6 patients

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fentanyl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICP (mmHg)</td>
<td>14.7 ± 3.4</td>
<td>15.9 ± 5.8</td>
<td>15.5 ± 4.7</td>
<td>13.6 ± 5.8</td>
<td>16.8 ± 5.6</td>
</tr>
<tr>
<td>CPP (mmHg)</td>
<td>84.1 ± 12.2</td>
<td>82.5 ± 9.9</td>
<td>86.6 ± 12.9</td>
<td>92.6 ± 11.9</td>
<td>92.5 ± 10</td>
</tr>
<tr>
<td>Methohexitone</td>
<td>3.1 ± 0.7</td>
<td>2.9 ± 0.4</td>
<td>3 ± 0.9</td>
<td>2.9 ± 1.5</td>
<td>2.9 ± 1.5</td>
</tr>
<tr>
<td>Methohexitone</td>
<td>40 ± 1.6</td>
<td>38.7 ± 12.5</td>
<td>34.9 ± 12.5</td>
<td>38.8 ± 7.6</td>
<td>37.1 ± 2.9</td>
</tr>
<tr>
<td>BIS</td>
<td>40 ± 16.7</td>
<td>38.7 ± 12.5</td>
<td>34.9 ± 12.5</td>
<td>38.8 ± 7.6</td>
<td>37.1 ± 2.9</td>
</tr>
<tr>
<td><strong>S(+)-ketamine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICP (mmHg)</td>
<td>15.9 ± 5.8</td>
<td>17.4 ± 4.1</td>
<td>16.8 ± 4.4</td>
<td>15.8 ± 4.4</td>
<td>16.8 ± 3.8</td>
</tr>
<tr>
<td>CPP (mmHg)</td>
<td>82.5 ± 9.9</td>
<td>11.4 ± 19</td>
<td>85.1 ± 12.9</td>
<td>92.5 ± 12.8</td>
<td>92.1 ± 12.8</td>
</tr>
<tr>
<td>Methohexitone</td>
<td>3 ± 0.9</td>
<td>2.9 ± 1.5</td>
<td>3 ± 0.7</td>
<td>2.9 ± 0.5</td>
<td>3 ± 0.8</td>
</tr>
<tr>
<td>Methohexitone</td>
<td>38.7 ± 12.5</td>
<td>38.8 ± 7.6</td>
<td>37.2 ± 7</td>
<td>38.4 ± 12.4</td>
<td>38.7 ± 2.3</td>
</tr>
<tr>
<td>BIS</td>
<td>38.7 ± 12.5</td>
<td>38.8 ± 7.6</td>
<td>37.2 ± 7</td>
<td>38.4 ± 12.4</td>
<td>38.7 ± 2.3</td>
</tr>
</tbody>
</table>

- Vasopressor requirement
  - Ketamine: norepinephrine 3.6 ± 5.1 mcg/kg/hr
  - Fentanyl: norepinephrine 12.8 ± 18.4 mcg/kg/hr

- Sedation
  - No difference in depth of sedation according to BIS between groups
  - Study terminated prematurely due to inadequate sedation
  - Ketamine (n=6) vs. fentanyl (n=4)

- Nutrition
  - No difference in time to full enteral nutrition or defecation

- No statistical difference in neurologic outcome
  - Ketamine GOS 2.0 vs. fentanyl GOS 2.6

**Conclusions**
Long-term sedation with S(+)-Ketamine/methohexitone does not increase ICP compared to fentanyl/methohexitone

**Strengths**
- Prospective, randomized trial
- All patients had ICP and CPP monitoring
- Data for continuous infusion over 5 days

**Limitations**
- Small patient population which did not meet power
- Half of patients withdrawn due to inadequate sedation
<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To compare cerebral hemodynamics of ketamine and sufentanil when used for sedation of severe head injury patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Prospective, randomized, double-blind trial in a single intensive care unit at a trauma center</td>
</tr>
</tbody>
</table>
| **Population**      | • Inclusion  
|                     |   ○ Patients 16-75 years old with TBI defined as: post-resuscitation GCS 3-8, who required mechanical ventilation and ICP monitoring and CT scan revealed significant risk of increased ICP  
|                     |   ○ Exclusion  
|                     |     ○ Life-threatening multiple injuries, kidney or heart insufficiency, hepatic failure, body weight of ≥ 130 kg, and history of psychosis |
| **Methods**         | • Patients were randomized by balanced eight-block sequence generated from randomization table  
|                     |   ○ Ketamine 50 mcg/kg/min (3 mg/kg/hr) and midazolam 1 mcg/kg/min (0.06 mg/kg/hr)  
|                     |   ○ Sufentanil 0.005 mcg/kg/min (0.3 mcg/kg/hr) and midazolam 1 mcg/kg/min (0.06 mg/kg/hr)  
|                     |   ○ Rates were adjusted to maintain ICP < 25 mmHg and CPP > 70 mmHg  
|                     | • Monitoring  
|                     |     ○ ICP, CPP, \( V_{MCA} \), MAP, HR, PaO\(_2\) saturation, end-tidal capnometry, GCS, pupillary response  
|                     | • Goals  
|                     |     ○ ICP < 25 mmHg  
|                     |     ○ CPP > 70 mmHg  
|                     |     ○ \( P_{aCO2} \) 35 ± 2  
|                     |     ○ Normothermia (37\(^\circ\))  
|                     |     ○ Head elevation 15\(^\circ\)  
|                     | • Nutrition  
|                     |     ○ Enteral nutrition began on day 1 and was increased by 500 mLs daily up to 2000 mLs per day  
|                     | • Neurologic outcomes (GOS) obtained at 6 months post-injury  
|                     | • Cost assessment  
|                     |     ○ Included drugs, tubing, and syringes per patient per day  
|                     | • Other values assessed  
|                     |     ○ Injury severity at baseline; use of neuromuscular blocking agents, thiopental, and propofol; volume replacement or vasopressor support; sedation efficacy during suction; and agitation medication requirement  
| **Statistics**      | • Data presented as mean ± SD  
|                     | • Quantitative factors assessed using analysis of variance when homogeneous and Kruskal-Wallis test when heterogeneous  
|                     | • Qualitative factors assessed using chi-square test or Fisher’s test  
|                     | • Statistical significance set at \( p < 0.05 \)  

G. Christina Caballero 14
### Results

- Ketamine (n=12) and sufentanil (n=13) populations were similar at baseline
  - Duration of sedation not significant (ketamine 6.2 ± 3.2 days vs. sufentanil: 5.3 ± 3.8 days)
- Mean infusion rate (days 1-4) similar
  - Ketamine: 82 ± 25 mcg/kg/min (4.9 mg/kg/hr)
  - Sufentanil: 0.008 ± 0.002 mcg/kg/min (0.48 mcg/kg/hr)
  - Midazolam 1.6 ± 0.5 mcg/kg/min (0.1 mg/kg/hr)
- Baseline ICPs higher in ketamine group (p = 0.07)
- CPP, ICP, and \( V_{MCA} \) were similar between groups
- Uncontrollable intracranial hypertension requiring additional sedation
  - Ketamine: 4 patients (propofol n=3, thiopental n=2)
  - Sufentanil: 4 patients (propofol n=4, thiopental n=1)
- Temperature, \( P_{aCO2} \), \( P_{aO2} \) saturation did not differ between groups throughout the sedation period
- Adjunct neuromuscular blocking agents
  - Ketamine (n=5) versus sufentanil (n=10)
- Mortality and neurologic outcomes
  - Death from intracranial hypertension
    - Ketamine (n=4) compared to sufentanil (n=3)
  - Rate of improvement of GCS after infusion discontinuation was faster in sufentanil group (p = 0.01)
  - GCS was similar at recovery between groups
  - Favorable GOS observed in 4 ketamine patients and 6 sufentanil patients
- Other outcomes
  - ICU stay
    - Ketamine: 21 ± 13 days
    - Sufentanil: 18 ± 13 days
  - Mean HR significantly higher in ketamine group on days 3 and 4 (p=0.03 and p=0.01 respectively)
  - Fluid administration was significantly less in ketamine patients on day 1 (p = 0.02)
  - Vasopressor requirement similar between groups
    - Ketamine: dopamine n=6, norepinephrine n=7
    - Sufentanil: dopamine n=8, norepinephrine n=11
  - Residual gastric volume and tolerance of enteral nutrition was similar between groups
  - Median daily cost per patient per day
    - Ketamine: 47 ± 13 US dollars
    - Sufentanil: 42 ± 14 US dollars

### Conclusions
- Ketamine in combination with midazolam is comparable with midazolam and sufentanil in maintaining intracranial pressure and cerebral perfusion pressure of severe head injury patient on mechanical ventilation

### Strengths
- Prospective, randomized trial
- All patients had ICP and CPP monitoring
- Clinical outcomes including ICU length of stay, mortality, and neurologic outcome assessed

### Limitations
- Small patient population that did not meet power
X. Conclusions
  a. Ketamine provides adequate sedation in combination with benzodiazepine or barbiturate therapy in TBI patients at doses ranging from 1 mg/kg/hr to 6 mg/kg/hr
  b. Ketamine may be associated with changes in ICP in severe TBI patients, although increases above 20 mmHg uncommon
  c. Insufficient data to recommend ketamine as first line therapy for sedation in TBI patients
  d. Patients who should get ketamine
     i. Cannot tolerate hypotension associated with alternative sedative therapy
     ii. Require adjunct therapy due to inadequate sedation with alternative agents
     iii. Potentially beneficial
         1. Inadequate pain control
         2. Reactive airway disease
         3. Hypotensive requiring vasopressor support
  e. Patients who should not get ketamine
     i. Refractory intracranial hypertension
     ii. Cardiovascular complications
         1. Myocardial infarction
         2. Tachyarrhythmia
         3. Hypertension
     iii. Contraindication to benzodiazepines or barbiturates as there is insufficient data to recommend ketamine monotherapy
XI. References

43. Stawicki SP. Sedation scales: very useful, very underused. OPUS 12 Scientist 2007;1:2:10-12.
Appendices

APPENDIX A. Glasgow Coma Scale Score (Range: 3-15)

<table>
<thead>
<tr>
<th>Motor Response</th>
<th>Verbal Response</th>
<th>Eye Opening</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Response = 1</td>
<td>No sounds = 1</td>
<td>No eye opening = 1</td>
</tr>
<tr>
<td>Extensor response, i.e. decerebrate</td>
<td>Incomprehensible sounds = 2</td>
<td>Eyes open to pain = 2</td>
</tr>
<tr>
<td>Motor Response</td>
<td>Verbal Response</td>
<td>Eye Opening</td>
</tr>
<tr>
<td>posturing = 2</td>
<td>Inappropiate words or jumbled phrases</td>
<td>Eyes open to speech = 3</td>
</tr>
<tr>
<td>Abnormal flexion, i.e. decorticate</td>
<td>consisting of words = 3</td>
<td></td>
</tr>
<tr>
<td>posturing = 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdraws from noxious stimuli = 4</td>
<td>Confused, yet coherent, speech = 4</td>
<td>Spontaneous eye opening = 4</td>
</tr>
<tr>
<td>Localizes to noxious stimuli = 5</td>
<td>Alert and Oriented = 5</td>
<td></td>
</tr>
<tr>
<td>Obey commands fully = 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APPENDIX B. Physiologic Parameters Relevant to Cerebral Perfusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Physiologic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Arterial Pressure (MAP)</td>
<td>70 – 105 mmHg</td>
</tr>
<tr>
<td>Cerebral Perfusion Pressure (CPP)</td>
<td>70 – 90 mmHg</td>
</tr>
<tr>
<td>Intracranial Pressure (ICP)</td>
<td>10 – 15 mmHg</td>
</tr>
<tr>
<td>Cerebral Blood Flow (CBF)</td>
<td>45 – 50 mL/100 g/min</td>
</tr>
<tr>
<td>Arterial Partial Pressure Oxygen (PaO₂)</td>
<td>80 – 100 mmHg</td>
</tr>
<tr>
<td>Arterial Partial Pressure Carbon dioxide (PaCO₂)</td>
<td>35 – 45 mmHg</td>
</tr>
</tbody>
</table>

APPENDIX C. Ramsay Sedation Scale

<table>
<thead>
<tr>
<th>Patient Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is anxious and agitated or restless, or both</td>
<td>1</td>
</tr>
<tr>
<td>Patient is co-operative, oriented, and tranquil</td>
<td>2</td>
</tr>
<tr>
<td>Patient responds to commands only</td>
<td>3</td>
</tr>
<tr>
<td>Patient exhibits brisk response to light glabellar tap or loud auditory stimulus</td>
<td>4</td>
</tr>
<tr>
<td>Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus</td>
<td>5</td>
</tr>
<tr>
<td>Patient exhibits no response</td>
<td>6</td>
</tr>
</tbody>
</table>
**APPENDIX D. Traumatic Coma Data Bank CT Scan Classification for Severe Head Injury**

<table>
<thead>
<tr>
<th>Severity of Injury</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>Diffuse injury</td>
<td>2</td>
</tr>
<tr>
<td>Diffuse injury with swelling</td>
<td>3</td>
</tr>
<tr>
<td>Diffuse injury with shift</td>
<td>4</td>
</tr>
<tr>
<td>Mass lesion surgically evacuated</td>
<td>5</td>
</tr>
<tr>
<td>Mass lesion not operated</td>
<td>6</td>
</tr>
</tbody>
</table>

**APPENDIX E. Hunt & Hess Classification of Subarachnoid Hemorrhage**

<table>
<thead>
<tr>
<th>Severity of Injury</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal headache or slight nuchal rigidity</td>
<td>Grade I</td>
</tr>
<tr>
<td>Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy</td>
<td>Grade II</td>
</tr>
<tr>
<td>Drowsy, confused, or have mild focal neurologic deficits</td>
<td>Grade III</td>
</tr>
<tr>
<td>Neurologic condition are those who are stuporous with moderate to severe hemiparesis, possibly early decerebrate rigidity, and vegetative disturbances</td>
<td>Grade IV</td>
</tr>
<tr>
<td>Deep coma with decerebrate rigidity or a moribund appearance</td>
<td>Grade V</td>
</tr>
</tbody>
</table>

**APPENDIX F. Glasgow Outcome Scale**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>1</td>
</tr>
<tr>
<td>Vegetative State (meaning the patient is unresponsive, but alive; a &quot;vegetable&quot; in lay language)</td>
<td>2</td>
</tr>
<tr>
<td>Severely Disabled (conscious but the patient requires others for daily support due to disability)</td>
<td>3</td>
</tr>
<tr>
<td>Moderately Disabled (the patient is independent but disabled)</td>
<td>4</td>
</tr>
<tr>
<td>Good Recovery (the patient has resumed most normal activities but may have minor residual problems)</td>
<td>5</td>
</tr>
</tbody>
</table>