Adequate sedation and analgesia is a basic, important measure in controlling ICP in both adult and pediatric patients with various intracranial pathological entities and reduced intracranial compliance. Deepening sedation is one of the routine first steps when ICP rises. The available sedative and hypnotic agents—opioids, benzodiazepines, propofol, and barbiturates—decrease blood pressure and may therefore decrease cerebral perfusion pressure (CPP). Ketamine is a potent, safe, rapid-onset anesthetic agent that does not decrease blood pressure. However, ketamine’s use in patients with traumatic brain injury and intracranial hypertension is precluded because it is widely stated that it increases intracranial pressure (ICP). Based on anecdotal clinical experience, the authors hypothesized that ketamine does not increase—but may rather decrease—ICP.

Methods. The authors conducted a prospective, controlled, clinical trial of data obtained in a pediatric intensive care unit of a regional trauma center. All patients were sedated and mechanically ventilated prior to inclusion in the study. Children with sustained, elevated ICP (> 18 mm Hg) resistant to first-tier therapies received a single ketamine dose (1–1.5 mg/kg) either to prevent further ICP increase during a potentially distressing intervention (Group 1) or as an additional measure to lower ICP (Group 2). Hemodynamic, ICP, and CPP values were recorded before ketamine administration, and repeated-measures analysis of variance was used to compare these values with those recorded every minute for 10 minutes following ketamine administration.

Results. The results of 82 ketamine administrations in 30 patients were analyzed. Overall, following ketamine administration, ICP decreased by 30% (from 25.8 ± 8.4 to 18.0 ± 8.5 mm Hg) (p < 0.001) and CPP increased from 54.4 ± 11.7 to 58.3 ± 13.4 mm Hg (p < 0.005). In Group 1, ICP decreased significantly following ketamine administration and increased by > 2 mm Hg during the distressing intervention in only 1 of 17 events. In Group 2, when ketamine was administered to lower persistent intracranial hypertension, ICP decreased by 33% (from 26.0 ± 9.1 to 17.5 ± 9.1 mm Hg) (p < 0.0001) following ketamine administration.

Conclusions. In ventilation-treated patients with intracranial hypertension, ketamine effectively decreased ICP and prevented untoward ICP elevations during potentially distressing interventions, without lowering blood pressure and CPP. These results refute the notion that ketamine increases ICP. Ketamine is a safe and effective drug for patients with traumatic brain injury and intracranial hypertension, and it can possibly be used safely in trauma emergency situations. (DOI: 10.3171/2009.1.PEDS08319)

Key Words • ketamine • sedation • intracranial pressure • child • intracranial hypertension • traumatic brain injury • cerebral perfusion pressure

See the corresponding editorial in this issue, pp 37–39.
Ketamine for intracranial hypertension

even mentioned in the 2007 adult guidelines for TBI and is hardly mentioned in the guidelines for the treatment of severe pediatric TBI. However, the evidence supporting the long-standing notion that ketamine increases ICP is rather limited. and several other studies actually refute it. Based on anecdotal experience, we hypothesized that ketamine does not increase—but may rather effectively decrease—ICP in patients with intracranial hypertension. The objective of this study was to prospectively analyze ICP and hemodynamic responses to ketamine administration in pediatric patients with elevated ICP.

Methods

Study Design

In this prospective, open, clinical trial we analyzed changes in ICP, hemodynamic variables, and CPP in response to ketamine administration in a before-after design, with each patient serving as its own control.

Patient Population

The study was performed in the PICU of the Rambam Medical Center, the tertiary care trauma center for Northern Israel, admitting all patients requiring neurosurgical care in the region. The institutional review board of the Rambam Medical Center approved the study, and the study protocol adhered to the principles set forth in the US Code of Federal Regulations (Title 45, Part 46, Protection of Human Subjects). Parents of enrolled patients signed an informed consent. The study has been registered at ClinicalTrials.gov (Protocol ID: KETICPCTIL).

All patients in whom intracranial hypertension had developed and in whom the condition was not responsive to first-tier and, in many instances also, second-tier measures were eligible for inclusion. Intracranial hypertension was defined as an ICP value > 18 mm Hg. Patients included in the study were divided into 2 groups according to the indication for ketamine administration: In Group 1, ketamine was administered to prevent further ICP increase during a potentially distressing intervention such as respiratory physiotherapy, endotracheal suctioning, bed linen or diaper change, and positional change; in Group 2, ketamine was administered as an additional measure to lower markedly elevated ICP.

Measurements and Interventions

Intracranial pressure, hemodynamic variables, and CPP were recorded 2 and 1 minute prior to and then every minute for 10 minutes following a single intravenous dose of 1–1.5 mg/kg of a racemic mixture of ketamine. A 10-minute observation period was chosen as ketamine is a short-acting drug with an action duration of ~10 minutes. No other therapeutic interventions or drug changes were allowed during this observation period. The potentially distressing intervention was started within 2–3 minutes of ketamine administration and was completed within the 10-minute observation period. A PICU physician was present at the patient’s bedside to immediately respond to a potentially hazardous increase in ICP or decrease in CPP following ketamine administration. All patients continued to be fully and closely monitored in the PICU after completion of the 10-minute observation period to rule out any late or rebound effects.

Statistical Analysis

Values are reported as the mean ± SD. Repeated-measures ANOVA was used to compare measurements recorded before and after ketamine administration. A p value of < 0.05 was considered statistically significant. Statistical calculations were performed using the Statistical Package for Social Sciences (Windows version 14.0).

Results

Thirty patients, aged 1–16 years, were included in the study between March 2005 and November 2007, and their demographic and clinical details are summarized in Table 1.

All patients were treated prior to inclusion in the study according to the guidelines for the treatment of severe pediatric TBI. All patients underwent mechanical ventilation and received basic anesthesia with a continuous infusion of midazolam (2–5 µg/kg/min) and morphine (20–50 µg/kg/hr). At the time of ketamine administration, 10 patients received additional sedation with a continuous infusion of propofol (1–4 mg/kg/hr) and 1 patient received a continuous infusion of atracurium for muscle paralysis. Twenty patients received hyperosmolar therapy (either mannitol or 3% NaCl) shortly before ketamine administration. Eleven patients underwent continuous infusion of thiopental (1–4 mg/kg/hr) at the time of some ketamine administrations, and in 9 patients ketamine was administered following decompressive craniectomy.

Ketamine was administered in 82 events: in 17 events the indication was the prevention of further ICP increase during a potentially distressing intervention (Group 1), and in 65 events the indication was attempted lowering of a markedly elevated ICP (Group 2).

On initial statistical analysis, the 2 sets of baseline values, recorded 2 and 1 minute prior to ketamine administration, were found to be almost identical, with no significant differences (paired t-test). Therefore, their mean values were used as the baseline for further analysis.

Following ketamine administration, ICP decreased within 2 minutes from 25.8 ± 8.4 to 18.0 ± 8.5 mm Hg (p < 0.001, repeated-measures ANOVA) (Fig. 1A), a 30% decrease from baseline. The CPP increased from 54.4 ± 11.7 to 58.3 ± 13.4 mm Hg (p < 0.005) (Fig. 1B). Neither MABP (Fig. 1C) nor pulse rate changed significantly. The decrease in ICP and the increase in CPP occurred within the first 2 minutes of ketamine administration and remained unchanged during the rest of the observation period. No rebound effects were noted beyond the 10-minute observation period.

In Group 1, mean ICP decreased from 25.2 ± 5.4 to 17.9 ± 5.5 mm Hg within the first 2 minutes of ketamine administration (p < 0.001) (Fig. 2). Subsequently, during the performance of the distressing activity, ICP increased slightly up to 19.6 ± 6.7 at Minute 7 and then decreased again. Hence, during the entire observation period, ICP remained lower by > 5 mm Hg compared with baseline
values, a 20% decrease. Despite the performance of a potentially distressing intervention, ICP decreased in 15 of 17 ketamine administrations, increased by up to 2 mm Hg in 1 of 17, and by > 2 mm Hg in only 1 of 17.

In Group 2, when ketamine was administered to lower persistent intracranial hypertension, ICP decreased sharply within the first 2 minutes from 26.0 ± 9.1 to 17.5 ± 9.1 mm Hg (p < 0.0001), a 33% decrease from baseline, and remained < 18 mm Hg from Minutes 4–10 of ketamine administration (Fig. 3A). The CPP increased from 54 ± 12 to 58 ± 14 mm Hg (p < 0.05) (Fig. 3B), and MABP decreased slightly, from 79 ± 11 to 75 ± 11 mm Hg (p < 0.05) (Fig. 3C). Intracranial pressure decreased in 61 of 65 ketamine administrations, increased by up to 2 mm Hg in 3 of 65, and increased briefly by > 2 mm Hg in only a single event.

Discussion
In this prospective clinical trial we intended to study the effects of ketamine on ICP in patients with intracranial hypertension, in light of the long-standing, deeply entrenched opinion that ketamine increases ICP.13,19,21,28,29,36,39

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TABLE 1: Demographic and clinical data in patients with intracranial hypertension who received ketamine

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Indication for Ketamine†</th>
<th>1st- &amp; 2nd-Tier Therapy‡</th>
<th>Sedatives, Hypnotics, &amp; Muscle Relaxants§</th>
<th>Etiology &amp; Major Neurosurgical Diagnoses</th>
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<tbody>
<tr>
<td>1</td>
<td>2, F</td>
<td>2</td>
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<td>MO, MID</td>
<td>FH; DAI</td>
</tr>
<tr>
<td>2</td>
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<td>OSM, TP</td>
<td>MO, MID</td>
<td>FH; SAH, rupture sagittal sinus</td>
</tr>
<tr>
<td>3</td>
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<td>2</td>
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<td>MO, MID, PROP</td>
<td>MVA; DAI</td>
</tr>
<tr>
<td>4</td>
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<td>TP</td>
<td>MO, MID, PROP</td>
<td>MVA; EPH, DAI, thalamic bleeding</td>
</tr>
<tr>
<td>5</td>
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<td>MO, MID</td>
<td>FH; EPH, DAI</td>
</tr>
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<td>6</td>
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<td>MO, MID</td>
<td>MVA; CC</td>
</tr>
<tr>
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<td>OSM</td>
<td>PROP</td>
<td>FH; CC</td>
</tr>
<tr>
<td>8</td>
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<td>2</td>
<td>OSM</td>
<td>MO, MID</td>
<td>FH; ICH, EPH</td>
</tr>
<tr>
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<td>MO, MID</td>
<td>foreign body penetration; ICH</td>
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<tr>
<td>11</td>
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<td>1, 2</td>
<td>DC</td>
<td>MO, MID</td>
<td>MVA; SDH, SAH, DAI</td>
</tr>
<tr>
<td>12</td>
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<td>2</td>
<td></td>
<td>MO, MID</td>
<td>FH; CC, DAI</td>
</tr>
<tr>
<td>13</td>
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<td>2</td>
<td>OSM, TP</td>
<td>MO, MID</td>
<td>FH; SDH, ICH, acute brain swelling, BSH</td>
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<tr>
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<td>MO, MID, PROP</td>
<td>MVA; CC, SDH</td>
</tr>
<tr>
<td>15</td>
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<td>MO, MID</td>
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<td>16</td>
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<td>MO, MID, PROP</td>
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<tr>
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<td>TP, DC</td>
<td>MO, MID</td>
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<td>19</td>
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<td>20</td>
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<td>MO, MID, PROP</td>
<td>MVA; SDH, CC</td>
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<td>MO, MID, PROP, TRC</td>
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<tr>
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<td>MO, MID</td>
<td>FH; CC</td>
</tr>
<tr>
<td>23</td>
<td>18, M</td>
<td>1, 2</td>
<td>TP</td>
<td>MO, MID</td>
<td>electrocution &amp; near drowning; brain edema</td>
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<td>MO, MID, PROP</td>
<td>MVA; SDH, DAI</td>
</tr>
<tr>
<td>25</td>
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<td>OSM, TP, DC</td>
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<td>T cell ALL; ICH</td>
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<tr>
<td>26</td>
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<td>1</td>
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<td>PROP</td>
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<td>27</td>
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<td>2</td>
<td></td>
<td>MO, MID</td>
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<tr>
<td>28</td>
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<td>1, 2</td>
<td>OSM, TRC</td>
<td>MO, MID</td>
<td>FH; SDH, EPH</td>
</tr>
<tr>
<td>29</td>
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<td>2</td>
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<td>FH; CC, DAI</td>
</tr>
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<td>30</td>
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<td>1, 2</td>
<td>OSM</td>
<td>MO, MID, PROP</td>
<td>AVM; ICH</td>
</tr>
</tbody>
</table>

* ALL = acute lymphocytic leukemia; AVM = arteriovenous malformation; BSH = brainstem herniation; CC = cerebral contusion; DAI = diffuse axonal injury; DC = decompressive craniectomy; EPH = epidural hematoma; FH = fall from height; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; MID = midazolam; MO = morphine; MVA = motor vehicle accident; OSM = hyperosmolar therapy (mannitol or 3% saline); PROP = propofol; SAH = subarachnoid hemorrhage; SDH = subdural hematoma; TP = thiopental; TRC = atracurium.
† Indication for ketamine: 1 = prevention of further ICP increase during a potentially distressing intervention; 2 = lowering of increased ICP.
‡ First- & second-tier therapy reflects measures applied to lower increased ICP at the time of ketamine administration.
§ Sedatives, hypnotics, and muscle relaxants were used as basic, first-tier TBI treatment protocol.
Based on preliminary observations, we hypothesized that ketamine will not only not increase ICP but that it may effectively reduce it and prevent potentially detrimental ICP elevations during distressing interventions in susceptible patients. Our results clearly show that in well-sedated, mechanically ventilated pediatric patients with intracranial hypertension—mostly due to TBI—our basic hypothesis is true, namely that ketamine decreases, rather than increases, ICP.

For the purpose of this study, we defined intracranial hypertension as sustained ICP > 18 mm Hg. This is our PICU’s “routine” threshold for the institution of ICP-lowering therapy, especially in younger children, as we have long realized that it enables us to more effectively prevent potentially detrimental, sustained ICP levels > 20 mm Hg.

Ketamine is a short-acting, fast-onset dissociative drug that induces effective sedation, analgesia, and anesthesia with a high safety margin. In its effective therapeutic range, it does not depress spontaneous ventilation and does not lower blood pressure. As such, ketamine would be an optimal drug for short interventions in emergency situations and in unstable patients.

The major listed contraindication to ketamine, which markedly restricts its use in emergency trauma situations and practically precludes its use in TBI, is its reported effect of increasing ICP. There seems to be a long-standing general consensus in the neurosurgery, surgery, anesthesia, pharmacology, emergency, and critical care literature that ketamine is contraindicated in patients who have, or may develop, intracranial hypertension. Both adult and pediatric guidelines for the treatment of TBI hardly mention ketamine in the chapters dealing with sedation and anesthesia.

The notion that ketamine increases ICP stems from several case reports and case series published mostly between 1970 and 1972, shortly after ketamine was introduced as an anesthetic agent in the mid-1960s. Increases in ICP were observed following administration of ≥ 2-mg/kg doses of ketamine for short diagnostic or surgical procedures in awake children and adults. Almost all of these ICP elevations were observed in patients with an obstructed ventricular system, mostly due to malfunctioning ventriculoperitoneal shunts or in those with no shunts at all. These elevations were observed in patients who were...
breathing spontaneously, although most of the reports stress that the patients continued to breath effectively and that their arterial or end-tidal PCO$_2$ did not increase. The ICP increased only in patients who had received ketamine as a sole anesthetic agent or who were only lightly anesthetized with nitrous oxide. The ICP did not increase when thiopental was administered before ketamine, and when thiopental was administered following ketamine-induced ICP elevation, ICP decreased promptly.

Subsequent clinical and laboratory studies did not support these initial observations. When used for the induction of anesthesia, intravenous administration of ketamine (3 mg/kg) to patients with no intracranial abnormalities resulted in jugular bulb venous pressure elevations of only 1.9 mm Hg (from 7 to 9 mm Hg), whereas MABP and CPP increased by 15.7 and 13.8 mm Hg, respectively. Belopavlovic et al. used midazolam or diazepam followed by a 1-mg/kg dose of ketamine for the induction of anesthesia in patients with brain tumors or hydrocephalus. The ICP increased by 8 mm Hg after midazolam/ketamine and by 3 mm Hg after diazepam/ketamine. Much sharper ICP elevations were observed during and after muscle paralysis and tracheal intubation, suggesting suboptimal sedation and anesthesia. Mayberg et al. found that ketamine did not elevate ICP or CBF velocity in patients undergoing craniotomy after induction of isoflurane/nitrous oxide anesthesia.

In patients with severe TBI who were sedated with propofol, Albanèse et al. found that ICP decreased following ketamine administration. In adult patients with severe TBI, Bourgoin et al. found no significant differences in the mean daily values of ICP and CPP or in the number of ICP elevations between patients in whom sedation was achieved with a continuous infusion of ketamine/midazolam or with sufentanil/midazolam. Similarly, Kolenda et al. compared ketamine/midazolam sedation with fentanyl/midazolam sedation in patients with moderate to severe TBI and found a lower requirement for catecholamines, higher CPP and only nonsignificant 2–mm Hg higher ICP values in the ketamine/midazolam group.

The initial observations of ICP elevations have been related to the cerebral metabolic rate–enhancing effect of ketamine, accompanied by a corresponding increase in CBF, as autoregulation is maintained during ketamine anesthesia. Other studies, however, have found no changes or even CBF decreases following ketamine administration. Measurements of CBF were not obtained in our study, and we do not know whether autoregulation has been fully maintained in our patients, in whom major brain pathological entities were present. Our findings of ICP decreases following ketamine are quite obviously not compatible with concurrent CBF increases.

The well-anesthetized, mechanically ventilated patients in this study differed markedly in that respect from the non- or lightly sedated patients described in the early reports. Anesthetics such as barbiturates, benzodiazepines, isoflurane/nitrous oxide, and propofol have been shown to blunt or eliminate the cerebral metabolic rate, CBF, and ICP increases associated with ketamine. We assume that this use of additional anesthetics accounts for the absence of ICP elevations following practically all ketamine administrations in our patients.

The more unexpected finding of our study is the clinically important and statistically significant decrease in ICP following ketamine. We presume that despite the rather deep sedation and anesthesia, including high-dose thiopental in more than a few instances, ketamine induced an additional potent anesthetic effect. Unfortunately, we performed neither cerebral function monitoring nor CBF measurements. This is a significant limitation of our study, and further research is required to elucidate the mechanism of the ICP-lowering effect of ketamine.

Interestingly, deepening sedation is hardly mentioned in the first- or second-tier treatment protocols for intracranial hypertension, although this is rather routinely undertaken in the daily ICU practice. Our findings highlight the efficacy of ketamine in achieving an ICP-lowering effect with practically no undesired side effects such as decreases in blood pressure or CPP.

Although our findings were observed in sedated, mechanically ventilated pediatric patients in the PICU setting, we believe that they may be applicable to other patient

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**Fig. 3.** Graphs showing ICP (A), CPP (B), and MABP (C) responses to ketamine administration in an attempt to lower markedly elevated ICP (65 events, Group 2). Intracranial pressure decreased by 33% within 2 minutes of ketamine administration. *p < 0.05, **p < 0.0001.
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populations and clinical scenarios: adult patients should respond in a similar manner as their cerebral hemodynamic and pharmacological responses are not different from those of children, and studies in adults support our findings. Ketamine, combined with a benzodiazepine, may be a preferred short-acting anesthetic in emergency situations and in trauma patients, including those with potential intracranial disease. Nevertheless, further laboratory and clinical research is needed before our observations can be generalized and before clear-cut recommendations can be made.

Conclusions

In patients with intracranial hypertension undergoing mechanical ventilation, ketamine effectively decreased ICP and prevented untoward ICP elevations during potentially distressing interventions, without lowering blood pressure and CPP. These results refute the notion that ketamine increases ICP. Combined with a benzodiazepine, ketamine may be the preferred sedative/anesthetic medication for patients with TBI and intracranial hypertension, and it can probably be used safely in trauma emergency situations.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References


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