Ketamine and Intracranial Pressure: No Contraindication Except Hydrocephalus

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Shortly after the 1970 introduction of ketamine, there appeared multiple worrisome reports of elevated intracranial pressure (Figure).[1-9] Many of the cited intracranial pressure values were significant—the largest increase was 1,600 mm H_2O[9]—and alarming sequelae included apnea and bradycardia. Anesthesiologists quickly abandoned ketamine in patients with neurologic disorders, and a contraindication in settings of possible intracranial pressure elevation subsequently appeared in anesthesiology textbooks and review articles, including patients with cerebral trauma, mass, or hemorrhage.[10]

Two decades later when ketamine revolutionized emergency department pediatric procedural sedation, this established contraindication was assumed to apply and was dutifully reproduced in emergency medicine reviews and textbooks.[11] Emergency physicians were fearful to use ketamine in disease states or for procedures with the potential for increased intracranial pressure, including lumbar puncture for suspected meningitis and rapid sequence intubation for trauma.

This sequence of events illustrates how clinical maxims can be quickly formed and promulgated and become dogma despite incomplete evidence, and how when such mandates are misguided it can take decades of research efforts and hand-wringing to reverse them. During these corrective periods, patients may be deprived of effective treatment options.

In hindsight, the well-intentioned 1970s anesthesiologists who encouraged this edict made 2 critical errors. First, it should have been recognized that the largest intracranial pressure elevations and all occurrences of sequelae requiring intervention occurred in patients with preexisting hydrocephalus (Figure). Among these patients, those with intact cerebrospinal fluid flow tolerated intracranial pressure increases without incident, as would be expected. Second, as early as 1972 it was recognized that ketamine increases intracranial blood flow through cerebral vasodilation, and despite absolute increases in intracranial pressure cerebral perfusion is maintained or improved.[12-15] These factors should have mitigated the concerns and prevented the extrapolation of the ketamine contraindication beyond those patients with known cerebrospinal fluid obstruction. As is always the case in medicine, there were doubters, and the subsequent literature includes a variety of case series and trials investigating ketamine in neurologic disorders, trauma, and critical care.

In this issue of *Annals*, Cohen et al[15] report a systematic review of 10 controlled trials of ketamine in mechanically ventilated adults and find no adverse measures of cerebral perfusion or adverse clinical outcomes. Also in this issue, Loflin and Koyfman[16] summarize a systematic review of 5 controlled trials of ketamine versus opioids for sedation, regardless of mechanical ventilation. Similarly, they found no adverse outcomes or increased intracranial pressure in patients receiving ketamine rather than opioids. Despite their overlap, the inherent limitations of a systematic review study design, and underlying study heterogeneity, these reviews constitute the best available evidence and support the safety of ketamine, even in critically ill patients.

The most fascinating and compelling of the single trials included in these reviews is that by Albanese et al.[14] These authors studied 8 mechanically ventilated adults with traumatic brain injury and measured intracranial pressure at baseline and then 2 minutes after sequential doses of ketamine at 1.5, 3, and 5 mg/kg intravenously, with a 6-hour washout between each dose. Thus, using each patient as his or her own control, they found no increases—indeed slight decreases—in intracranial pressure at all 3 doses studied and found consistent maintenance of cerebral perfusion pressure.

Myth debunking is hardly new with regard to ketamine. The early anesthesiologists who were concerned about ketamine's effect on intracranial pressure also advised that it should be routinely coadministered with a benzodiazepine and an anticholinergic. The intent of these adjuncts was to mitigate distressing recovery reactions and problematic airway secretions, respectively.[10] Both of these maxims were later disproved when it was shown that there was no benefit to midazolam prophylaxis in children[17-20] and no increase in airway problems or clinically important secretions when an anticholinergic was omitted.[20-23] Other historical concerns—enhanced laryngospasm risk with minor oropharyngeal procedures and in children aged 3 to 12 months—have similarly been shown to have been substantially overstated.[20,22,23]

So after 45 years of experience with ketamine, what do we know? This sympathomimetic drug can certainly elevate intracranial pressure, but it can also decrease it. More important, the crucial measure of cerebral perfusion pressure is not adversely affected, and there are no reported cases of patients actually experiencing resulting harm, excepting those with structural barriers

1969 Tjaden[1]	Fifty children underwent ketamine-assisted pneumoencephalography with "consistent" but unreported elevations of ICP; none had sequelae.
1971 Evans[2]	Four children undergoing ketamine-assisted neurodiagnostic procedures were noted to have ICPs of 210 to 300 mm H_2O; none had sequelae.
1971 Gardner[3]	Eleven healthy adults had ICP increases with ketamine, averaging 253 mm H_2O and ranging up to 433 mm H_2O; none had sequelae.
1972 Gibbs[4]	Six of 9 adults with intracranial space-occupying lesions had an average of 12 mm Hg ICP increases after ketamine; none had sequelae.
1972 List[5]	An infant with hydrocephalus and a "flat" fontanelle was given ketamine; shortly thereafter, apnea ensued, with a "tense and bulging" fontanelle. Treatment included ventricular puncture and drainage of cerebrospinal fluid. Seven subsequent children with hydrocephalus had ICP measured before and after ketamine; the increases averaged 247 mm H_2O and ranged up to 550 mm H_2O; none had sequelae.
1972 Lockhart[6]	Two infants with symptomatic hydrocephalus developed apnea and bradycardia shortly after intramuscular ketamine and required intubation.
1972 Shapiro[7]	Five children with ventriculostomies were noted to have ICPs increase by an average of 42 mm Hg after ketamine was administered, with increases ranging up to 60 mm Hg. They were treated with mask hyperventilation and thiopental.
1972 Wyte[8]	One child with obstructive hydrocephalus had an ICP increase from 8 to 72 mm Hg after ketamine; he was treated with thiopental.
1975 Crumrine[9]	Twenty-six children underwent ventriculostomy revision; 25 were noted to have ICP elevations ranging from 2 to 8 times baseline (highest increase 1,600 mm H_2O), peaking a mean of 4 minutes after ketamine. Several were treated with CSF removal, but no other treatment or sequelae are described.

Figure. Early case reports and small case series of intracranial pressure elevation with ketamine. *ICP*, Intracranial pressure; *CSF*, cerebrospinal fluid.

to normal cerebrospinal fluid flow. In the absence of evidence of such obstruction, emergency physicians should freely consider using ketamine for otherwise-indicated procedural sedation, rapid sequence intubation, and analgesia in the critically ill. It is time to put this ketamine maxim in perspective and declare it yet another misstep in the colorful lore of this unique drug.

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