



KETAMINE GUIDELINE FOR ICP CONTROL IN ADULTS

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I. Guideline for use of Ketamine in Increased ICP:

No ketamine therapy should ever be instituted for ICP management without the Neuro-ICU faculty approval. Ketamine is to be ordered by a physician or midlevel provider on behalf of Neuro-ICU faculty once approval is received. Therapy must always be supervised by Neuro-ICU faculty to include all bolus dosing and drip titration (bolus dosing for rapid sequence induction used during intubation is separate from this guideline)

A. Patient Requirements & General Recommendations:

1. All of these patients must be intubated, with adequate ventilator support and respiratory monitoring.
2. All of these patients must have ICP monitoring (EVD and or parenchymal monitor).
3. CPP must be monitored with a goal CPP of 60-80 mmHg. If the CPP remains above 80 mmHg for greater than one hour and an upper CPP limit has not been established, a physician must be notified.
4. Once ketamine is started, opioids, and barbiturates should be slowly weaned to either a minimum dose or completely off.
5. Ketamine should be started with a benzodiazepine (midazolam) intravenous drip to prevent emergence reactions (hallucinations and vivid dreams).
6. Recommend EEG monitoring for the first 48 hours during ketamine induction and withdrawal to assess the degree of cortical suppression.
7. Ketamine therapy for increased ICP is initiated with a bolus dose followed by a continuous drip. Bolus therapy alone is not therapeutic and does not allow for a steady state.
8. If a total of ketamine 4 mg/kg has not decreased ICP (to include the initial and repeat bolus) consider alternative treatment.
9. Ketamine therapy is not the first line treatment for increased ICP. It is usually started after hyperosmolar therapy or in conjunction with this therapeutic modality.

10. Ketamine therapy can be combined with mild to moderate controlled hypothermia therapy for refractory elevated ICP.
11. Continuous cardiac ECG monitoring is required during ketamine use. Patients may also require continuous cardiac output and cardiac index monitoring (invasive or non-invasive) secondary to the potential cardiovascular side effects of ketamine use.
12. Beta blockers are the antihypertensive of choice for hypertension, intracranial hypertension, or tachycardia especially if ketamine doses are > 80 mcg/kg/min.
13. Use IBW for dose calculations. (In morbidly obese patients LBW is recommended).[1] A separate IV pump may be required for administration of this medication if the weight used for titration is different than any other titrating drip on the same pump system.

B. Induction of Ketamine Therapy (Faculty/physician supervised):

1. Initial bolus dose is 1-2 mg/kg over 1 minute and must be administered by a physician or midlevel provider (for all new drips).
2. Start a ketamine IV infusion immediately after the bolus dose with a concentration of 5000 mg/500 ml NS at 16 to 24 mcg/kg/min.

C. Maintenance of Ketamine Therapy (Faculty/physician supervised):

1. If ICP is elevated to > 20 for more than 5 minutes, continue to bolus ketamine with 1-2 mg/kg every 5-10 minutes if needed. If a total of 4 mg/kg has not decreased ICP (to include the initial and repeat bolus) consider alternative treatment.
2. Concomitant with ketamine is an infusion of midazolam or lorazepam
 - a. Midazolam: 0.02-0.1 mg/kg/hr (decrease dose by 50% for elderly patients or those with CrCl <10ml/min).
 - b. Lorazepam: 0.01-0.1 mg/kg/hr (recommended for patients with hepatic dysfunction).
3. After each bolus dose, increase the ketamine drip by 8 to 16 mcg/kg/min.
4. ICP should be controlled on average with doses between 50 and 80 mcg/kg/min.
5. Use caution if the ketamine dose needs to be increased beyond 80 mcg/kg/min. Faculty should be notified if doses higher than 80 mcg/kg/min are required. The maximum dose is 116 mcg/kg/min. [2]; [3]

D. Weaning of Ketamine Therapy (Faculty/physician supervised):

1. Once an order has been obtained for weaning, wean ketamine by 8 mcg/kg/min every 4 hours as indicated and tolerated by patient.
2. Increase the ketamine drip back to the previous dose/rate if there is a rebound and ICP is again increased.

3. May require catecholaminergic support such as norepinephrine if hypotension is noted after removing all antihypertensive medications. May require addition of midodrine prior to attempting or reattempting to wean off ketamine.
4. Wean benzodiazepines once ketamine has been weaned completely off.

II. Background:

Ketamine is a dissociative anesthetic agent that inhibits the sensory association areas of the cortex, components of the limbic system, and thalamus.[4] Ketamine was considered contraindicated for patients with increased ICP until recently. [5] Case series like the one published by Shapiro et al (1972) supported that idea. However, most of those 7 patients had CPPs less than 60 at the time and had hydrocephalus. New literature started to surface especially in the pediatric population where ketamine was used to effectively control ICP. Pilot studies using ketamine for increased ICP including patients with severe TBI are supporting the idea that ketamine may be useful for the treatment of increased ICP. [6], [7], [8], [9] Ketamine appears to suppress the spreading depolarization, which can induce further secondary brain injury in TBI patients. [10]

A. Main Effects:

1. Noncompetitive antagonist of the central nervous system NMDA receptors: [11] [12], [13], [3]
 - a. NMDA receptors are a calcium-gated channel receptor
 - b. NMDA receptor agonists are excitatory amino acids: glutamic acid, aspartic acid, and glycine. They bind to the receptor, and induce the opening of this ion channel causing neuronal depolarization.
 - c. The intracellular calcium entry from the activation of these channels is associated with neurotoxicity and cell death.
 - d. NMDA receptors are involved in the sensory input at the spinal, thalamic, limbic, and cortical levels.
2. Ketamine blocks sensory input and impairs limbic functions (the association of sensory inputs with emotions). [14]
3. Agonist at alpha and beta adrenergic receptors can increase the systemic blood pressure and heart rate. Ketamine increases cerebral perfusion pressure (CPP). [11], [15]
4. Antagonism at muscarinic receptors (mAChR) of the central nervous system may explain some of the cognitive side effects like hallucinations and vivid dreams.
 - a. M1 mAChRs are the most abundant mAChR subtype in the CNS. They are abundant in the cortex, hippocampus, striatum and thalamus (post-synaptically). [16]
 - b. M2 mAChRs are located mainly in the brainstem and thalamus, also in the cortex, hippocampus and striatum (in the cholinergic synaptic terminals and may control the release of ACh). [16]
 - c. M3 and M5 mAChRs are expressed at much lower levels than M1 or M2 mAChRs in the CNS. M3 mAChRs are found in the cortex and hippocampus. M5 mAChR are found in the substantia nigra. [16]
 - d. M4 mAChRs are found in the cortex and hippocampus, but are most abundant in the striatum, where they are thought to play a role in controlling dopamine

release and locomotor activity. [16]

5. Agonist at opioid sigma receptor may also be involved in the hallucinogenic side effects of ketamine.

B. Pharmacokinetics:

1. Onset of action 30 seconds.
2. Elimination half life 2.5 hours. [11]
3. Liver biotransformation CYP450 system with norketamine as the major metabolite. Norketamine has 1/3 of the anesthetic potency of ketamine. The majority of norketamine is hydroxylated and conjugated to form a water-soluble compound, which is readily secreted in the urine and to a much lesser extent in the feces. [11]

C. Adverse Effects:

1. Emergence reactions such as hallucinations and vivid dreams have been reported. [11]
 - a. Combination therapy with a benzodiazepine minimizes this effect.
 - b. The combination of ketamine – midazolam was reported to be more effective than ketamine-diazepam in reducing emergence reactions and had less effect in prolonging recovery. [17]; [18]
2. Ketamine has been reported to produce skeletal muscle hypertonicity and rigidity. In addition, many patients demonstrate random head or extremity movements unrelated to noxious stimulation. [11]
3. Ketamine has bronchodilatory effects. Salivary and tracheobronchial secretions may be increased by ketamine. [11]
4. Ketamine is a mild respiratory depressant. [11]
5. Ketamine blocks catecholamine reuptake and may produce cardiovascular side effects such as tachycardia and hypertension. [5]

D. Precautions:

1. Systolic blood pressure > 180
2. Acute or subacute cardiac dysfunction
3. Vascular dissection

III. References:

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