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# Emergency Medicine Pharmacotherapy with Resuscitation (EMPowerRx) Conference





# The ketamine controversy: ketamine and intracranial pressure in rapid Sequence intubation

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# Disclosures

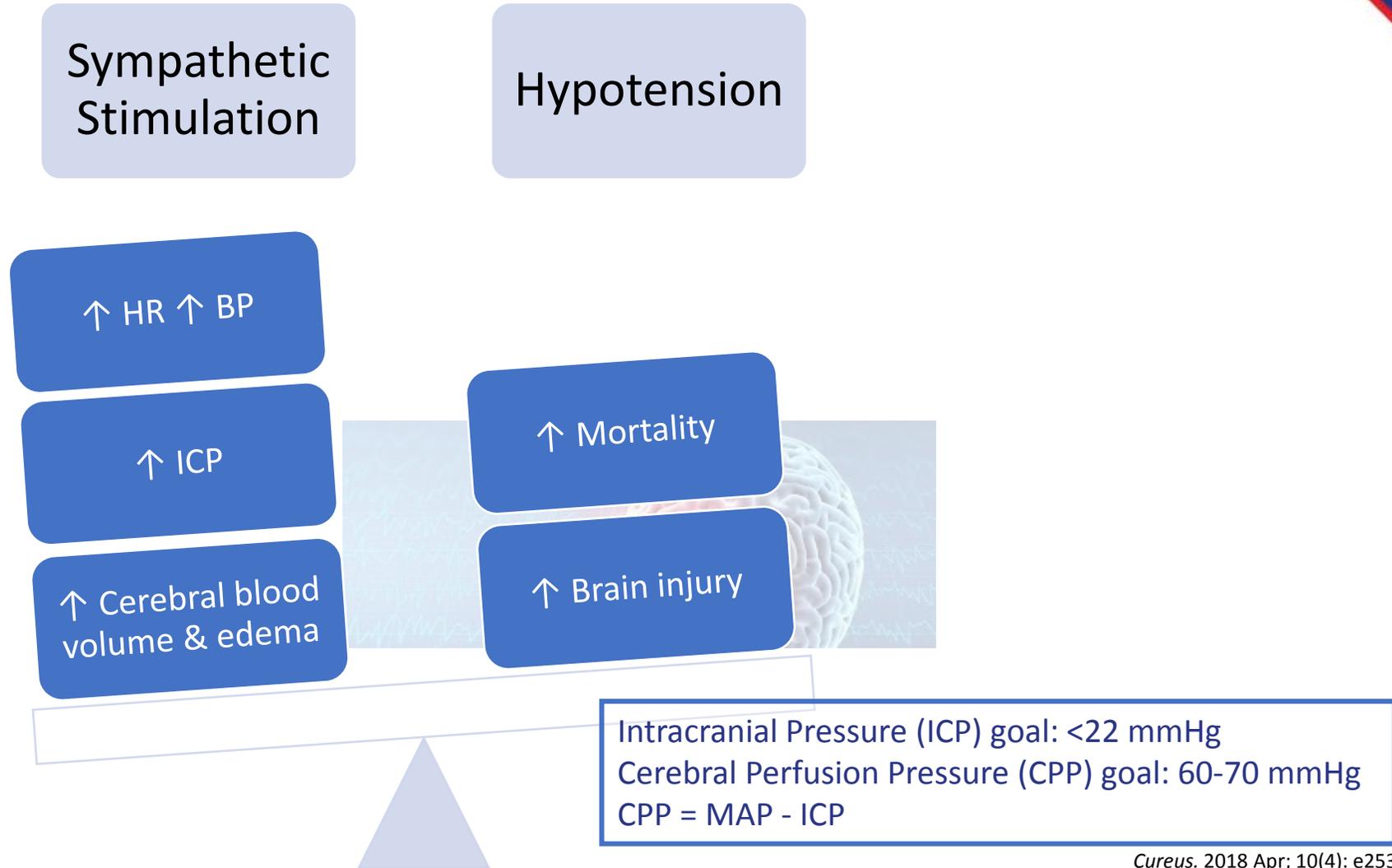
- I have no financial disclosures or conflicts of interest related to the content of this presentation



# Learning Objective

- Outline the relevant literature surrounding ketamine and intracranial pressure (ICP) in rapid sequence intubation (RSI)

# RSI in TBI: a balancing act



Cureus. 2018 Apr; 10(4): e2530.

# Background on ketamine

Ketamine becomes approved by the FDA

Multiple case studies published on ketamine and ICP

1970

1971

1972

1995

First study evaluating ketamine's effect on CSF pressure

First randomized prospective study evaluating ketamine and ICP

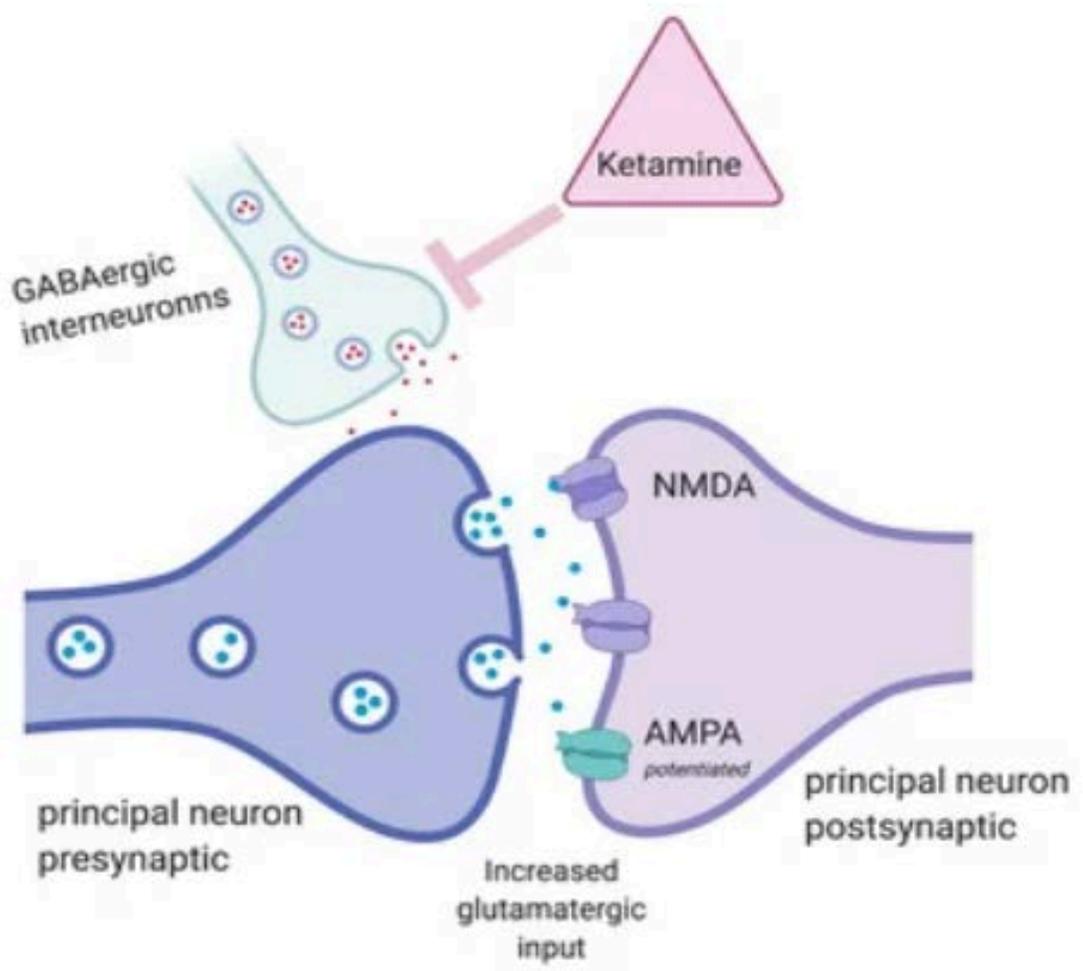
*Neurocrit Care.* 2014; 21:163–173.  
*Anesthesiology.* 1971; 35:226-8.

# Ketamine overview

Mechanism of Action	Dose	Pharmacokinetics	Hemodynamic Effects	Precautions/Contraindications
<ul style="list-style-type: none"><li>• NMDA receptor antagonist</li></ul>	<ul style="list-style-type: none"><li>• 1-2 mg/kg IV push</li></ul>	<ul style="list-style-type: none"><li>• Onset: 30-60 seconds</li><li>• Duration: 5-15 minutes</li></ul>	<ul style="list-style-type: none"><li>• ↑ HR</li><li>• ↑ BP</li><li>• ↑ MAP</li></ul>	<ul style="list-style-type: none"><li>• Glaucoma</li><li>• Ocular trauma</li><li>• Psychiatric disease</li></ul>

*Emerg Med Clin N Am.* 2008 Nov; 26(4):1043–1068.

# The proposed mechanism



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graph TD; A[Nitric oxide synthase inhibition] --> B[Small vessel vasoconstriction]; B --> C[↑ Cerebral oxygen extraction]; D[↑ PCO2] --> E[Large vessel vasodilation];
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Anesth Analg. 2005;101:524-34.

# THE “SUPPORTING” EVIDENCE

Study:	Patients:	ICP:	CPP:
Gardner, et al. 1971 Case-control	<ul style="list-style-type: none"> <li>- 11 healthy males for simple surgery</li> <li>- Receiving ketamine 2 mg/kg IV</li> </ul>	↑	↑
Gibbs, et al. 1972 Case-control	<ul style="list-style-type: none"> <li>- 11 healthy patients for lumbar discectomy; second arm 9 patients with intracranial space lesions</li> <li>- Receiving ketamine 1-1.3 mg/kg IV</li> </ul>	↔ / ↑	↑
Shapiro, et al. 1972 Case-control	<ul style="list-style-type: none"> <li>- 7 patients; including 5 with external shunts and ↑ ICP</li> <li>- Receiving ketamine 2 mg/kg IV or 4 mg/kg IM</li> </ul>	↑	↔
Kolenda, et al. 1996 Prospective RCT	<ul style="list-style-type: none"> <li>- 35 patients with moderate-severe head injury</li> <li>- Sedation with ketamine + midazolam vs fentanyl + midazolam</li> </ul>	↑	↑

# Kolenda H, et al.

## Intervention

- Prospective randomized control trial evaluating moderate-severe TBI patients who received continuous infusions of ketamine and midazolam or fentanyl and midazolam

## Patients (n=35)

- Average patient was a Caucasian male between 30-38 years old with a GCS of 3-8; 12 patients received ketamine/midazolam and 12 received fentanyl/midazolam for continuous analgo-sedation
- Nine patients were withdrawn during treatment due to persistent ICP above 25 mmHg

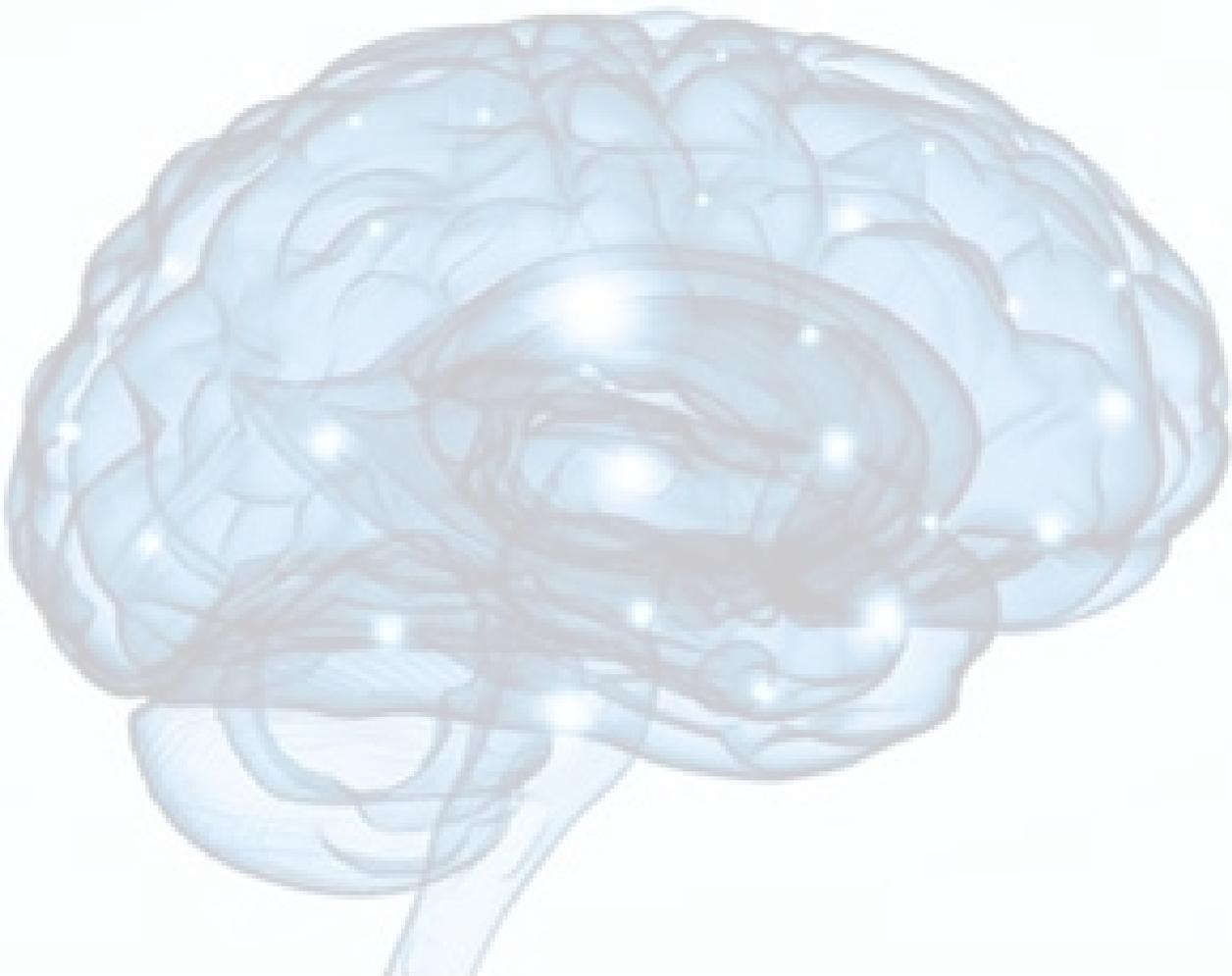
## Outcomes

- Median ICP was 2 mmHg higher in the ketamine group (14.6 mmHg) compared to fentanyl (significant findings on day 8 and 10;  $p < 0.05$ )
- CPP was higher in the ketamine arm (80.5 mmHg) compared to fentanyl (72.3 mmHg)

## Conclusion

- In patients with moderate to severe TBI, ICP and CPP values were found to be slightly higher with ketamine than fentanyl, but overall there was no difference in terms of ICP control

*Acta Neurochir (Wien). 1996;138:1193-9.*



# The rebuttal

# More Recent Literature On The Matter

Study	Patients	Intervention	Results
<p>Bourgoin, et al. 2005</p> <p><i>Prospective, double-blind RCT</i></p>	<p>Adult patients with severe TBI receiving sufentanil/midazolam or ketamine/midazolam (n=30)</p>	<p>Sufentanil/midazolam vs. Ketamine/midazolam (rates doubled for 15 min)</p>	<ul style="list-style-type: none"> <li>No difference was found in mean ICP or mean CPP during 15 minutes compared to sufentanil</li> <li>No elevations in ICP related to ketamine</li> </ul>
<p>Schmittner, et al. 2007</p> <p><i>Prospective, randomized trial</i></p>	<p>Adult patients with severe TBI or aneurysmal subarachnoid hemorrhage (n=24)</p>	<p>Methohexitone plus either: Fentanyl 3 mcg/kg bolus and infusion x5 days vs. Ketamine 0.5 mg/kg bolus and infusion x5 days</p>	<ul style="list-style-type: none"> <li>No difference in mean daily ICP between ketamine and fentanyl</li> <li>No difference found in mean daily CPP between ketamine and fentanyl</li> </ul>

*Crit Care Med.* 2005;33:1109-13.

*J Neurosurg Anesthesiol.* 2007;19:257-62.

# Mayberg TS, et al.

## Intervention

- Prospective trial evaluating neurosurgical patients requiring a craniotomy who received a 1 mg/kg bolus of ketamine

## Patients (n=35)

- Average patient was 49 years old, 78 kg; 10 patients had supratentorial tumors while 10 had intracranial aneurysms; patients all received ketamine 1 mg/kg bolus along with co-interventions thiopental, nitrous oxide and isoflurane to maintain anesthesia
- Ventilation was controlled (PaCO<sub>2</sub> 34 ± 1 mmHg)

## Outcomes

- ICP decreased from 16 ± 1 mmHg to 14 ± 1 mmHg for the first 10 minutes (p < 0.001)
- No difference was observed in CPP following ketamine bolus over 10 minutes

## Conclusion

- In ventilated neurosurgical patients with mildly increased ICP and anesthetized with isoflurane and nitrous oxide, ketamine did not increase either MAP, CPP or ICP

*Anesth Analg.* 1995;81:84-9.

# Summary

Study:	Ketamine Administration:	ICP:	CPP:
Mayberg, et al. 1995  Prospective	- Ketamine 1 mg/kg IV bolus	↓	↔
Kolenda, et al. 1996  Prospective RCT	- Continuous infusion (65 mg/kg/day)	↑	↑
Bourgoin, et al. 2005  Prospective RCT	- Continuous infusion, rate doubled for 15 minutes	↔	↔
Schmittner, et al. 2007  Prospective RCT	- Ketamine 0.5 mg/kg bolus and infusion x5 days	↔	↔

CJEM. 2010;12(2):154-7.

Annals of Emergency Medicine. 2015;65(1): 43-51.

# Recommendations

The available data suggests ketamine does not adversely effect intracranial pressure or cerebral perfusion pressure

Based on its pharmacological properties, ketamine should be considered as a safe induction agent for RSI in patients with head-injury



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