Ketamine or Etomidate for RSI?

Key Article

Machett G, et al. Etomidate versus ketamine for emergency endotracheal intubation: a randomized clinical trial. Intensive Care Medicine. 2022; 48: 78-91.

Background

- Etomidate and ketamine are often used to provide sedation during RSI in the ED
- A number of observational studies have been published over the past decade examining the risks and benefits of both
- In 2020, the NEAR Cohort registry study found an increased rate of hypotension and need for vasopressors with **ketamine** when compared to etomidate in patients with sepsis, no difference in patients with trauma.
- The most rigorous evidence we had so far was a 600+ patient RCT in France found no statistical difference in rates of hypotension between 0.3 mg/kg of Etomidate vs. 2mg/kg Ketamine in critically ill patients requiring RSI
- Current clinical practice guidelines recommend either agent for RSI in patients with shock,
- This past month, an additional RCT was published, and asked the question, "Is there a difference in Day 7 (or short-term) survival when critically ill patients are intubated using Etomidate vs. Ketamine?"

Trial Design & Setting

- Prospective, randomized, open-label trial performed over a 4-year period
- Single-center (UT-Southwestern Medical Center)
- RSI was performed by dedicated Anesthesia Airway Team – that is separate from clinical ICU teams
- Screening for enrollment was based on clinical opinion of Airway Team Lead – if there was a belief that one drug would be more appropriate, that patient was not enrolled
- **Inclusion criteria:** Adult patient needing RSI
- **Exclusion criteria:** Pregnant women, children, previously enrolled patients, patients requiring awake intubation, neurologically obtunded patients, and cardiac arrest patients.
- Powered to detect a 10% difference in Day 7 survival if 750 patients were enrolled, allowed to enroll up to 825 with the assumption of a 10% dropout rate.

Interventions

- Medications: Etomidate 0.2 – 0.3 mg/kg IV or Ketamine 1-2mg/kg IV
    - Doses were allowed to be adjusted based on provider clinical judgement
- Airway interventions: Variable and at the discretion of the airway team, but generally
    - Head up (20-30 degree) positioning
    - Pre-oxygenation
    - Use of neuromuscular blocking agent
    - Use of intubating stylet

- Use of cricoid pressure
- Confirmation with end-tidal CO2
- Treatment of post-intubation hypotension with bolus-dose vasopressors and IV fluids

Trial Endpoints

- Primary: Day 7 survival
- Secondary: Proportion survived on Study Day 28, duration of mechanical ventilation, ICU length-of-stay, vasopressor requirement, new diagnosis of adrenal insufficiency Day 1-4 after intubation, and SOFA scores

Results

- A total of 801 critically ill patients were enrolled between 2016 – 2020
  - **Out of 1,952 patients screened for eligibility, 1,151 patients were excluded**
    - 446 patients were obtunded or were in cardiac arrest
    - In 309 patients, the clinical team made a decision to use another medication for sedation (opioid, benzodiazepine, propofol)
    - There was unstable clinical circumstances or clinician preference not to enroll in 396 patients
    - This is worth discussing later on
  - Because this was an EFIC study (enrolled prior to consent), 4 etomidate and 6 ketamine patients withdrew from the study after enrollment, leaving…
  - A total of 801 patients
    - Ketamine: 395 patients
    - Etomidate: 396 patients
- About 50% of patients in this trial were diagnosed with Sepsis before or immediately post-intubation
- Most patients were intubated on the medical floors
- Characteristics were generally equal between groups, worth noting:
  - Mean MAP pre-intubation was 80-85 mmHg
  - ***Mean Etomidate dose used: 0.2 mg/kg***
  - ***Mean Ketamine dose used: 1.2 mg/kg***
  - Direct laryngoscopy used in ~50%
  - First pass success in 91%
  - Rocuronium was used primarily as the Neuromuscular blocking agent (~80% of patients)
- **Primary Outcome: Day 7 Survival was higher in the Ketamine group (85.1%) compared to the Etomidate group (77.3%);** *p=0.005*
  - Patients in the etomidate arm were 1.6 times more likely to die compared to the ketamine group.
- Day 28 survival?
  - 64.1% etomidate vs. 66.8% ketamine, no statistical significance
- *Secondary* outcomes: No difference in any, including diagnosis of adrenal insufficiency
- *Exploratory* outcomes worth noting:
  - Post-intubation hypotension requiring bolus vasopressors was more common in patients receiving ketamine compared to those who received etomidate, but did not require more continuous vasopressor infusions overall

Discussion points

- Peri-intubation hypotension in the ketamine group aligns with date from previous National Emergency Airway Registry Database study (Performed by our EM-CCM colleague Nick Mohr), and multiple other smaller observational studies among patients with shock.
    - It's notable that this occurred even with a reduced dose of ketamine in patients with a higher mean baseline MAP
    - It's unclear however, if the patients who did become hypotensive, were under-resuscitated, had a lower baseline MAP, or other unrecognized hemodynamic issue to begin with. This may have simply been a patient selection issue.
- Survival: This study was powered to find a difference between 7-day survival, which it did!
    - Should we take anything away from the fact that the difference didn't persist at Day 28?
    - Probably not. There are tons of confounders and clinical changes (including withdrawal of life sustaining therapies) that could occur based on factors not controlled by this trial.
- There was a lot of clinical autonomy and decision making around whether:
    - A. to enroll
    - B. what dose to use
- This was a single center, open label trial which does limit some of the generalizability of these findings.
- It also was not an "ED Study" although the patients appear to be very similar to those we take care of on a day to day basis.

Take home points

- Patients who received ketamine for RSI had a greater 7-day survival than patients who received Etomidate in this single-center RCT
- Peri-intubation hypotension may be more common when using ketamine for RSI compared to etomidate, even in reduced dosing so be prepared to use push-dose pressors
- The decision about sedation agent for RSI still should be patient specific, but more evidence to suggest that ketamine may have better short-term outcomes than etomidate