Etomidate in pediatric rapid sequence intubation: GABA, GABA doo or GABA, GABA don’t?

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Learning Objectives:

1. Review steps and considerations for rapid sequence intubation (RSI)
2. Explain anatomical and physiologic considerations for pediatric RSI
3. Describe medications used in RSI
4. Identify the controversial use of etomidate in the pediatric population
5. Analyze pediatric safety and efficacy literature for etomidate in pediatric RSI
Airway compromise is the most common cause of mortality in acutely ill and injured children\textsuperscript{1}

RSI provides a method for emergent airway placement
I. Purpose

A. Airway management is a primary provider role in the emergency department (ED)

B. RSI is preferred method for emergent intubation in patients with varying levels of consciousness and presumed to have a full stomach

C. Process designed to quickly secure an airway in patients requiring assisted ventilation

D. With appropriate technique, RSI’s success rate is 98.5%

II. Indications for RSI

III. RSI Procedure Overview

A. Streamlined process to ensure consistent placement of an emergent airway

B. The “6 P’s”

1. Assess patient for potentially difficult airway
2. Ensure appropriate equipment is available at bedside
3. Connect patient to necessary monitors and gain intravenous access
4. Verify requested medications based on patient-specific factors

Preoxygenate

1. Tight-fitting non-rebreather oxygen mask for 3-5 minutes
2. Achieve optimal oxygen stores
3. Provides nitrogen wash-out
4. Reserve bag mask ventilation for patients not breathing spontaneously

Airway manipulation with laryngoscope and endotracheal tube can increase heart rate (HR), intracranial pressure (ICP), blood pressure (BP), and airway resistance

Pre-treatment with atropine, lidocaine, muscle relaxants, and opiates may attenuate these reactions
Pre-treat

4. Administer sedative prior to paralytic
   • Give neuromuscular blocker
   • Base drug selection on patient-specific characteristics

Paralytic

5. Place endotracheal (ET) tube
   • Connect tube to ventilator
   • Check for appropriate placement (listen for gastric/breath sounds, watch for chest rise, check end-tidal CO₂, obtain chest X-ray)

Place tube

6. Inflate cuff and secure ET tube
   • Establish waveform capnography monitoring
   • Provide continued pain and sedation therapy

Post-intubation care

IV. Physiologic responses to RSI¹
   A. Elicit cough and gag reflexes
   B. Tachycardia and hypertension
   C. Hypoxia
   D. Elevation in ICP and intraocular pressure
   E. Bradycardia

V. Unique considerations in the pediatric population¹²⁻³⁹
   A. Anatomy and physiology in infants and children vary compared to adults (See Appendix A and B for detailed description of pediatric anatomical and physiologic considerations in RSI)
      1. Larger tongues, tonsils, and adenoids
      2. Shorter, narrower trachea
      3. Prominent occiput, superior larynx, and floppy epiglottis
      4. Increased chest wall compliance leads to respiratory fatigue and failure
      5. Age-related respiratory rate
      6. Preferential nasal breathing
      7. Lower functional residual capacity
      8. Higher oxygen metabolism
      9. Increased respiratory fatigue
     10. Higher vagal tone

RSI Medication Review

VI. Ideal pharmacokinetic properties for RSI medications¹,³
VII. Pre-medications\textsuperscript{1-3}
   A. Administered to reduce anxiety and prevent negative physiologic responses to RSI
   B. Optimal timing is medication dependent
   C. Atropine
      1. May be used for pediatric patients who experience bradycardia from ET tube placement or succinylcholine administration
      2. American Heart Association recommendations for use in RSI
         a. All patients < 1 year
         b. Patients 1-5 years receiving succinylcholine
         c. Pediatric patients > 5 receiving subsequent doses of succinylcholine

<table>
<thead>
<tr>
<th>Table 1: Atropine drug information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>0.02 mg/kg</td>
</tr>
<tr>
<td>Max: 0.5 mg</td>
</tr>
<tr>
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<td></td>
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</tbody>
</table>

D. Lidocaine
   1. May reduce adrenergic and physiologic responses to laryngoscopy and ET tube placement
   2. May reduce ICP so may be considered for patients with traumatic brain injury (TBI)

<table>
<thead>
<tr>
<th>Table 2: Lidocaine drug information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>1.5 mg/kg</td>
</tr>
<tr>
<td>Max: 100 mg</td>
</tr>
</tbody>
</table>

VIII. Induction Agents\textsuperscript{1-3,40}
   A. Unless completely unconscious, sedate all patients prior to paralytic administration
   B. Many sedatives have been used for RSI in the pediatric population
   C. Administration of sedative agent several minutes prior to paralytic is typically preferred to assure drug has taken effect
      1. Exception: short-acting sedatives can be given immediately after to provide longer sedation
   D. Barbiturates\textsuperscript{1-3}
1. Gamma-amino butyric acid (GABA) receptor agonists
   a. Low dose: decrease GABA dissociation from the receptor
   b. High dose: directly stimulate GABA receptor
2. Traditionally, thiopental was used frequently for RSI induction due to its rapid onset, short duration, and ability to decrease ICP
3. Introduction of other medications, side effect profile, and drug shortages have now limited barbiturate use
4. Common side effects
   a. Respiratory depression
   b. Hypotension (myocardial depression and venodilation)
   c. Histamine-release
   d. Bronchospasm
   e. Hiccups
   f. Twitching
E. Benzodiazepines
   1. Reversible, non-competitive GABA receptor agonist
   2. Midazolam and diazepam have been utilized for RSI in children
   3. Advantages include amnestic, anti-convulsant, and anxiolytic properties
F. Ketamine
   1. Introduced in 1970
   2. Dissociative anesthetic agent
   a. Creates a functional dissociation between cortex and limbic system
   b. Dissociative properties are dose-dependent
   3. Quick onset, analgesic effects, short duration, favorable respiratory and hemodynamic profile make it an ideal drug for RSI

<table>
<thead>
<tr>
<th>Table 3: Drug information for various sedatives used in RSI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>Propofol</td>
</tr>
<tr>
<td>Fentanyl</td>
</tr>
</tbody>
</table>

Robinson 6
IX. Neuromuscular blocking agents (NMBA’s)\textsuperscript{1–3}
   A. Paralytic agents provide muscle relaxation for intubation
   B. Depolarizing agents
      1. Succinylcholine
         a. Two acetylcholine molecules coupled together
         b. Extended depolarization from prolonged interaction with acetylcholine receptor causes rapid fatigue of the muscle and refractory stimulation
         c. Adverse effects:
            (1) Muscle fasciculations
            (2) Hyperkalemia
            (3) Increased ICP
            (4) Bradycardia and asystole
            (5) Diffuse muscle pain
         d. Contraindications:
            (1) Known or suspected hyperkalemia
            (2) History or family history of malignant hyperthermia
            (3) Long-standing neuromuscular disease—myotonia, paraplegia, muscular dystrophy
            (4) Trauma or burns occurring > 3 days prior to medication use
   C. Non-depolarizing agents\textsuperscript{1–3}
      1. Fewer adverse effects than succinylcholine but longer duration of action
      2. Rocuronium
         a. Steroid-based, structural derivative of vecuronium
         b. Larger volume of distribution (V\textsubscript{d}) accounts for shorter duration compared to vecuronium
      3. Vecuronium
         a. Not ideal for RSI due to long onset and duration of action

| Table 4: Drug information of NMBA’s used in RSI |
|-----------------------------------------------|-----------------|-----------------|-----------------|--------------------|-----------------|
| Agent                                    | Dose (IV)       | Onset (seconds) | Duration (minutes) | Advantages                      | Disadvantages              |
| Succinylcholine                           | 1-2 mg/kg       | 30-60           | 3-5               | Rapid onset & short duration    | Hyperkalemia, ↑ ICP & IOP, HTN |
| Rocuronium                               | 0.6-1.2 mg/kg   | 30-90 (dose dependent) | 25-35           | Rapid onset                     | Longer duration             |
| Vecuronium                               | 0.1-0.2 mg/kg   | 60-120          | 35-75             |                                | Slower onset and longer duration; needs reconstitution |
IOP: intraocular pressure; HTN: hypertension

Etomidate Review

X. History of etomidate\textsuperscript{41-48}
   A. Past use of etomidate
      1. 1972
         a. Approved in Europe
         b. Used for endotracheal intubation and continuous sedation in mechanically ventilated patients
      2. 1983\textsuperscript{42}
         a. Approved in United States
         b. Startling series of deaths in multi-trauma ICU patients raised concern and prompted investigation
         c. Additional studies revealed adrenal suppression during continuous infusion
         d. Etomidate’s indication for continuous sedation was withdrawn

XI. Mechanism of action\textsuperscript{42,49}
   A. Carboxylated imidazole derivative
   B. Ultrashort-acting, non-barbiturate sedative agent
   C. Acts centrally through GABA receptor stimulation and depression of reticular activating system

XII. Adverse effect profile
   A. Hemodynamically neutral
      1. Decreased hypotension risk
      2. Decreased cardiac event risk
   B. Neuro-protective effects
      1. Reduces ICP through a decrease in cerebral blood flow and O\textsubscript{2} consumption
         a. Bramwell et al.\textsuperscript{49} found single-dose etomidate use in pediatric patients with severe TBI resulted in significant ICP reduction
      2. Maintains cerebral perfusion pressure
      3. Can be utilized in trauma population with head injuries
   C. Adrenocortical suppression\textsuperscript{40}
      1. 11-β hydroxylase enzyme inhibition reduces cortisol, aldosterone, and cortisone production
      2. Adrenal suppression duration, following one dose, varies between studies
         a. Duthie et al.\textsuperscript{50} demonstrated decreased plasma cortisol levels 1 hour post etomidate induction but no difference at 24 hours
         b. Absalom et al.\textsuperscript{51} & Donmez et al.\textsuperscript{52} reported decreased cortisol levels that continued at 24 hours
         c. Vinclain et al.\textsuperscript{53} studied 40 patients and reported adrenal insufficiency in 80% at 12 hours, 9% at 48 hours, and 7% at 72 hours following one induction etomidate dose
Table 5: Etomidate drug information

<table>
<thead>
<tr>
<th>Dose (IV)</th>
<th>Onset of Action (seconds)</th>
<th>Duration of Action (minutes)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg/kg</td>
<td>5-15</td>
<td>5-15</td>
<td>Minimal respiratory &amp; CV effects; ↓ ICP</td>
<td>Adrenal suppression</td>
</tr>
</tbody>
</table>

The Debate Behind Etomidate

XIII. Previously, etomidate was the “gold standard” for RSI in pediatrics\textsuperscript{54,55}
   A. Hemodynamically neutral
   B. Neuro-protective

XIV. Consistently, most significant concern is adrenocortical suppression\textsuperscript{50-53}

XV. American Academy of Pediatrics Resuscitation Guidelines\textsuperscript{56} state “etomidate should not be routinely used when intubating an infant or child with septic shock”
   A. In support of their recommendation, the guidelines cite two studies\textsuperscript{57-58}

Table 6: Trial summaries for etomidate use in septic shock patients

<table>
<thead>
<tr>
<th>n</th>
<th>Population</th>
<th>Results</th>
<th>Author Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>499</td>
<td>• 96 adult patients received etomidate • 403 adult patients did not receive etomidate</td>
<td>Mortality at 28 days: • Etomidate group—42.7% • Non-etomidate group—30.5%</td>
<td>Increased risk of mortality in patients who receive etomidate for induction</td>
</tr>
<tr>
<td>n</td>
<td>Population</td>
<td>Results</td>
<td>Author Conclusion</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------------</td>
<td>------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>60</td>
<td>23 received etomidate for induction</td>
<td>• Etomidate patients had ↓ cortisol, ↑ ACTH, &amp; ↑ 11-deoxycortisol levels</td>
<td>One single intubation dose negatively influences adrenal function for at least 24 hours and may increase death risk</td>
</tr>
<tr>
<td></td>
<td>• 8 were intubated without etomidate</td>
<td>• 7/8 children who died received etomidate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 29 were not intubated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

XVI. As a result, abandoning etomidate use entirely has been recommended\(^{50-61}\)

“\textit{The most appropriate behavior is preventing this drug-induced adrenal insufficiency and related consequences by withdrawing etomidate from the intensive care unit}”

“It is not unheard of for drugs to be ostracized for a number needed to harm of many thousands. Etomidate’s number needed to harm is 8. And no, you cannot give it to only the next seven patients and feel safe!”

XVII. However, is there a pediatric population that would benefit from etomidate?

**Clinical Question**

Should we use etomidate in ALL pediatric RSI? OR Should we abandon it completely? OR Are there populations where etomidate is safe?

XVIII. Considerations for etomidate use in non-septic pediatric patients undergoing RSI

A. Is it safe?
B. Is it efficacious?

XIX. Safety and efficacy overview for etomidate use in pediatrics

A. Etomidate has been studied in pediatrics in a variety of settings (See Appendix C for trial summaries of pediatric etomidate use in maintenance anesthesia and procedural sedation)
There are no prospective, randomized control trials comparing etomidate to another agent in pediatric RSI.

### Table 7: Trial summaries of literature review

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>n</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokolove et al.(^{62})</td>
<td>Retrospective</td>
<td>100</td>
<td>No evidence of clinically important adrenal suppression</td>
</tr>
<tr>
<td>Guldner et al.(^{41})</td>
<td>Retrospective</td>
<td>105</td>
<td>Minimal hemodynamic changes and low risk for clinically important adrenal suppression</td>
</tr>
<tr>
<td>Zuckerbraun et al.(^{63})</td>
<td>Prospective</td>
<td>101</td>
<td>Provided successful RSI with varied hemodynamic effects with low incidence of seizure</td>
</tr>
</tbody>
</table>

### Table 8: Trial summary of Sokolove et al. The safety of etomidate for emergency rapid sequence intubation of pediatric patients. *Pediatr Emerg Care* 2000;16:18-21.\(^{62}\)

#### Objective
Assess if pediatric patients receiving etomidate for RSI in the ED develop clinically important adrenal insufficiency or hypotension

#### Design/Methods
- Retrospective, multi-center chart review
- Comprised of pediatric patients from UC Davis Medical Center (UCDMC) ED from July 1992-November 1996 and Children’s Medical Center of Dallas (CMCD) from March 1995-May 1997

#### Patient Population
**Inclusion criteria:**
- UCDMC identified patients through ED billing records and CPT procedure code for endotracheal intubation
- CMCD identified patients through pharmacy billing records for etomidate

**Exclusion criteria:**
- > 10 years old
- Intubated prior to ED arrival
- Received multiple doses of etomidate

**Hospital standards of care:**
- UCDMC had no protocol for induction agent choice; midazolam often used
- CMCD only used etomidate in trauma patients

#### Endpoints/Outcomes

**Endpoints**
- Reason for intubation
- Etomidate dose
- Vital signs prior and within 20 minutes of RSI
- Exogenous steroid use

**Outcomes**
- Clinically important hypotension
  - ↓ in SBP to below one SD of mean normal for age
- Clinically important adrenal insufficiency
  - Need for exogenous steroid for suspected adrenal insufficiency during hospital stay
Baseline Characteristics

- 100 patients (<10 years) underwent RSI with etomidate
  - UCDMC [n]=56
  - CMCD [n]=44
- 59% male
- Mean age of 4.4 ± 3.0 years (range 1 month-9.7 years)

Results

- Intubation indication

<table>
<thead>
<tr>
<th>Trauma</th>
<th>Status Epilepticus</th>
<th>Pulmonary</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>72%</td>
<td>13%</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

- Mean etomidate dose was 0.37 ± 0.15 mg/kg (range 0.05-0.9 mg/kg)
- BP measurements prior and within 20 minutes were recorded in 84 patients
  - Mean change in BP was a decrease of 1 mmHg
    [95% CI -6 to +7 mmHg, p=0.83]
  - Mean change as percentage of normal BP for age was a decrease of 1%
    [95% CI -7% to +6%, p=0.82]
  - 4 patients exhibited decrease in BP to below one SD
    - 1 due to blood loss, 1 had recurrent hypotension throughout hospitalization, and 2 patients had transient hypotension
- 14/100 patients (14%) received steroids during hospitalization but none were for suspected adrenal insufficiency

Author’s Conclusion

- One time etomidate doses do not result in clinically important adrenal suppression with a low incidence of clinically important hypotension
- Prospective comparison studies are needed to further evaluate etomidate safety in the pediatric population

Strengths

- Pediatric population
- Sufficient etomidate dose
- Low missing data rate

Critique

- Descriptive study (no comparator group)
- Indirect adrenal function measure
- Did not report intubation success

Take away

- Trauma was primary indication for intubation
- Hemodynamically neutral in pediatric population
- No evidence of clinically significant adrenal insufficiency
- Intubation success not addressed


Objective

Evaluate frequency of immediate adverse effects (vomiting, seizures, myoclonus), hemodynamic effects, and delayed adverse events (adrenal suppression and persistent seizures)

Design/Methods

- Retrospective, single-center chart review
- Included patients from a university tertiary care, level 1 trauma center, hospital ED between July 1996-April 2001

Patient Population

- Inclusion criteria:
  - Identified patients through pharmacy logs and hospital billing records
Documented etomidate administration for RSI in ED

**Exclusion criteria:**
- > 10 years old

**Hospital standards of care:**
- Induction agent was physician discretion but etomidate was typical practice

**Endpoints**
- Patient demographics
- Indications for RSI
- Etomidate dose
- Vital signs prior to and within 10 minutes of etomidate induction for RSI
- Vomiting within 10 minutes of receiving etomidate
- Attempts required to intubate
- Intubation failures
- Documentation of seizures, myoclonus, and other complications
- Corticosteroid use

**Baseline Characteristics**
- 105 patients (< 10 years) underwent RSI with etomidate
- 54% male
- Mean age (+SD) of 3 (+2.9) years (range 43 days-10 years)

**Results**
- Indication for intubation

<table>
<thead>
<tr>
<th>Trauma</th>
<th>Respiratory Distress</th>
<th>AMS/Gag reflex loss</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>57%</td>
<td>20%</td>
<td>13%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- Median etomidate dose was 0.32 (+0.12) mg/kg
- Only 48% had documentation on intubation attempt #
  - 45% intubated on 1st attempt
  - 34% intubated on 2nd attempt
  - 18% intubated on 3rd attempt
  - 2% intubated on 4th attempt
- Only 49.5% had documentation of pre and post etomidate BP readings
  - The mean change in SBP was an increase of 4 mmHg [95% CI -3.3 to 9.2 mmHg]
  - The mean change in DBP was an increase of 7 mmHg [95% CI -3.1 to 11 mmHg]
- Only 71.4% had documentation of pre and post etomidate heart rate (HR)
- 4/105 (3.8%) intubations had immediate adverse events documented

<table>
<thead>
<tr>
<th>Age</th>
<th>Indication for RSI</th>
<th>Etomidate Dose</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr</td>
<td>Blunt head injury</td>
<td>0.4 mg/kg</td>
<td>Transient desaturation</td>
</tr>
<tr>
<td>5 yrs</td>
<td>Blunt head injury</td>
<td>0.24 mg/kg</td>
<td>Vomiting</td>
</tr>
<tr>
<td>2 yrs</td>
<td>Blunt head/chest injury</td>
<td>0.27 mg/kg</td>
<td>Vomiting</td>
</tr>
<tr>
<td>3 yrs</td>
<td>Blunt head/chest injury</td>
<td>0.3 mg/kg</td>
<td>Vomiting</td>
</tr>
</tbody>
</table>
Corticosteroid use

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
</table>
| Received steroids during hospitalization | 38/105 | 36.2%
| Indications for steroid use        |     |     |
| Non-adrenal suppression indications* | 38/38 | 100% |
| Presumed adrenal insufficiency     | 0/38 | 0%

Cortisol Levels

- No documented laboratory testing for adrenal insufficiency

*Wean from ventilator (n=20); reactive airway disease (n=8); increased ICP (n=4); other (n=6)

- 4/105 (3.8%) patients developed seizures after etomidate
  - All 4 patients had previous seizure history
- No patients developed status epilepticus during admission

**Author’s Conclusion**

- Etomidate produces minimal hemodynamic changes and has low risk for clinically important adrenal suppression, myoclonus, or seizures
- Association between etomidate and emesis is unclear
- Consider etomidate for patients who will tolerate minimal changes in BP

**Strengths**

- Pediatric population
- Assessed intubation success

**Critique**

- High missing data rate
- Lack of documentation was construed as absence of adverse events
- Seizures not detected by EEG
- Cortisol levels not drawn

**Take away**

- Primary indication for RSI was trauma
- Hemodynamically neutral in pediatric population
- Etomidate was associated with minimal adverse events
- Most patients achieved successful intubation within 2 attempts
- Poor data collection limits interpretation

### Table 11: Trial summary of Zuckerbraun et al. Use of etomidate as an induction agent for rapid sequence intubation in a pediatric emergency department. *Acad Emerg Med 2006;13:602-9.*

<table>
<thead>
<tr>
<th>Objective</th>
<th>Prospectively evaluate etomidate efficacy and safety in pediatric RSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design/Methods</td>
<td>Prospective, observational, single-center study</td>
</tr>
<tr>
<td></td>
<td>Included patients at an urban, tertiary care pediatric ED and level I trauma center between January 1, 2003 and December 31, 2003</td>
</tr>
<tr>
<td></td>
<td>Data on RSI conditions and complications were collected prospectively</td>
</tr>
<tr>
<td></td>
<td>ED hemodynamic data and inpatient data were collected retrospectively</td>
</tr>
<tr>
<td>Patient Population</td>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td></td>
<td>All patients &lt; 21 years</td>
</tr>
</tbody>
</table>
Outcomes
- Intubation indication
- Medications used/etomidate dose
- Intubation attempts
- Medication side effects (myoclonus, pain, seizure activity, hemodynamic instability, or blood, secretions, or vomit in the airway)
- Use and indication for corticosteroid administration
- Cortisol levels
- Clinical suspicion of adrenal suppression
- Hemodynamic data (mean maximal percent increase [MMPI], mean maximal percent decrease [MMPD] in SBP, DBP, and HR)

Baseline characteristics
- 77 patients were intubated with etomidate and underwent RSI
- The mean (±SD) age was 8.2 (±6.2) years (range 18 days-21 years)
- 55% male

Results
- Primary indication for intubation

<table>
<thead>
<tr>
<th>AMS</th>
<th>Respiratory Failure</th>
<th>Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=54</td>
<td>n=21</td>
<td>n=2</td>
</tr>
<tr>
<td>70.1%</td>
<td>27.3%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

- Primary ED diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>32</td>
<td>41.6</td>
</tr>
<tr>
<td>Seizure</td>
<td>16</td>
<td>20.8</td>
</tr>
<tr>
<td>Shock</td>
<td>15</td>
<td>19.5</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td>6</td>
<td>7.8</td>
</tr>
<tr>
<td>Overdose</td>
<td>5</td>
<td>6.5</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3.8</td>
</tr>
</tbody>
</table>

- Vecuronium was the NMBA used for 76/77 intubations (98.7%)
- The mean (±SD) etomidate dose was 0.31 (±0.07) mg/kg
- Intubation success

<table>
<thead>
<tr>
<th>Intubation success by attempt</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED intubation with ET tube</td>
<td>77</td>
<td>100</td>
</tr>
<tr>
<td>Data available on # of attempts</td>
<td>73/77</td>
<td>94.8</td>
</tr>
<tr>
<td>1st attempt</td>
<td>48/73</td>
<td>65.8</td>
</tr>
<tr>
<td>2nd attempt</td>
<td>17/25</td>
<td>23.3</td>
</tr>
<tr>
<td>3rd attempt</td>
<td>6/8</td>
<td>8.2</td>
</tr>
<tr>
<td>4 or more attempts</td>
<td>2/2</td>
<td>2.7</td>
</tr>
</tbody>
</table>

- Intubation conditions, complications, and side effects

<table>
<thead>
<tr>
<th>Conditions</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data available</td>
<td>69/77</td>
<td>89.6</td>
</tr>
<tr>
<td>Successful intubation conditions</td>
<td>68/69</td>
<td>99</td>
</tr>
<tr>
<td>Blood in airway</td>
<td>6/69</td>
<td>8.7</td>
</tr>
<tr>
<td>Emesis in airway</td>
<td>2/69</td>
<td>2.9</td>
</tr>
<tr>
<td>Secretions in airway</td>
<td>2/69</td>
<td>2.9</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>0/77</td>
<td>0</td>
</tr>
<tr>
<td>Brief generalized seizure activity</td>
<td>3/77</td>
<td>3.9</td>
</tr>
</tbody>
</table>
### Results continued

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMPD in SBP &gt; 20%</td>
<td>12/69</td>
<td>17.4</td>
</tr>
<tr>
<td>SBP ↓ meeting PALS hypotension definition</td>
<td>7/12</td>
<td>10.1</td>
</tr>
<tr>
<td>PALS hypotension requiring intervention*</td>
<td>2/7</td>
<td>2.9</td>
</tr>
<tr>
<td>MMPI in SBP &gt; 20%</td>
<td>26/69</td>
<td>38</td>
</tr>
<tr>
<td>MMPD in DBP &gt; 20%</td>
<td>13/68</td>
<td>19</td>
</tr>
<tr>
<td>MMPI in DBP &gt; 20%</td>
<td>32/68</td>
<td>47</td>
</tr>
<tr>
<td>MMPI in HR &gt; 20%</td>
<td>30/73</td>
<td>41</td>
</tr>
<tr>
<td>MMPD in HR &gt; 20%</td>
<td>14/73</td>
<td>19</td>
</tr>
</tbody>
</table>

*Hemorrhagic shock requiring blood; septic shock requiring fluids & vasopressors

- Hemodynamics in decompensated shock vs. non-shock at intubation
  - Decompensated shock had lower MMPD in SBP compared to non-shock patients (2.5% vs. 11%)
  - Decompensated shock had higher MMPI in SBP compared to non-shock patients (68.3% vs. 16.4%)

- Corticosteroid use

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received steroids during hospitalization</td>
<td>29/77</td>
<td>37.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications for steroid use</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-adrenal suppression indications*</td>
<td>21/29</td>
<td>72.4</td>
</tr>
<tr>
<td>Presumed adrenal insufficiency</td>
<td>8/29</td>
<td>27.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cortisol Levels</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal random cortisol levels</td>
<td>1/8</td>
<td>12.5</td>
</tr>
<tr>
<td>Low random cortisol levels</td>
<td>7/8</td>
<td>87.5</td>
</tr>
</tbody>
</table>

*Stridor (n=9); asthma (n=4); baseline medication (n=4); other (n=4)

### Author’s Conclusion

- Etomidate provided successful RSI conditions
- Hypotension and seizures were uncommon and occurred in patients with confounding diagnoses
- Use with caution in patients with adrenal insufficiency

### Strengths

- Pediatric population
- Assessed safety and efficacy of etomidate use
- Low missing data rate

### Critique

- Descriptive study (no comparison group)
- Cortisol level timing was inconsistent
- Single-center study design
- Shock etiology not reported

### Take away

- Primary indication for RSI was trauma
- Etomidate use is likely safe in other populations
- Difficult to draw conclusions on etomidate in septic shock patients based on results in this trial

### Conclusion & Recommendation
XXI. Summary
   A. The most common indication for RSI in our studies was trauma\textsuperscript{41,62,63}.
   B. The recommendation to avoid etomidate use in septic shock pediatric patients is based on the outcome in 23 pediatric patients\textsuperscript{56}.
   C. Single dose etomidate safety has been shown in non-shock pediatric populations\textsuperscript{41,62-63,66-70}.

XXII. Unanswered questions
   A. Is etomidate safe in patients with septic shock?
   B. Should steroids be administered to patients at risk for adrenal insufficiency who receive etomidate?

XXIII. Future study and developments
   A. Randomized controlled trial would improve strength of recommendation
   B. Carboetomidate may offer a hemodynamically neutral induction agent without adrenal insufficiency\textsuperscript{65}.
      1. Synthetic version of etomidate designed to avoid adrenal dysfunction
      2. Studies indicate it provides adequate sedation with minimal inhibition of 11β-hydroxylase
      3. Not available on market

XXIV. Recommendations
   A. Consider etomidate in pediatric population in RSI for trauma
      1. Trauma patients comprised largest population in pediatric safety and efficacy trials
      2. Etomidate was hemodynamically neutral with low seizure and adrenal insufficiency incidence
   B. Consider etomidate in pediatric medicine patients undergoing RSI
      1. Medicine patients comprised reasonable portion of Guldner and Zuckerbraun studies
      2. They displayed similar hemodynamic response if they did not present in shock
      3. If unable to rule out septic shock from clinical presentation/story, select alternative agent
   C. Select another induction agent for RSI in children with:
      1. Septic shock
         a. Direct causal effect between etomidate and poor outcomes has not been definitively proven
         b. However, it is wise to avoid adrenal suppression in patients unable to mount their own physiological stress response
      2. Risk for adrenal insufficiency
         a. Chronic steroid use/abrupt withdrawal
         b. Genetic conditions (Congenital adrenal hyperplasia is most common)
         c. Infection (septic shock)
   D. Administer 0.3 mg/kg IV for adequate sedation

Appendix A
Table 12: Anatomical considerations in pediatric patients

<table>
<thead>
<tr>
<th>Anatomic Feature</th>
<th>Result</th>
<th>Influence on RSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prominent occiput12,13</td>
<td>Causes varying degrees of neck flexion in supine position</td>
<td>Can result in airway obstruction or interfere with visualization of glottic opening</td>
</tr>
<tr>
<td>Large tongue14,15</td>
<td>Large tongue relative to oral cavity size</td>
<td>Can impede visualization of deeper airway or cause upper airway obstruction</td>
</tr>
<tr>
<td>Large tonsils and adenoids16</td>
<td>Increased mass of lymphoid tissue</td>
<td>Can result in airway obstruction and adenoidal bleeding/aspiration</td>
</tr>
<tr>
<td>Superior laryngeal position17,18</td>
<td>Larynx position is opposite C3-C4 in children compared to C4-C5 in adults</td>
<td>The acute angle between the glottic opening and base of tongue can make direct visualization more difficult</td>
</tr>
<tr>
<td>Large floppy epiglottis19</td>
<td>Epiglottis projects into the airway and covers more of glottic aperture; particularly in children &lt; 3 years</td>
<td>Use of straight blade to directly lift epiglottis improves visualization</td>
</tr>
<tr>
<td>Shorter and more narrow trachea20-23</td>
<td>Trachea increases in length as children age from ~5 cm in neonates to 12 cm in adults</td>
<td>Predisposes patient to right mainstem bronchus intubation or inadvertent extubation</td>
</tr>
<tr>
<td>Anatomic subglottic narrowing24-27</td>
<td>Cricoid ring is most narrow portion of airway in pediatric patients</td>
<td>ET tube may be small enough to pass through the vocal cords but not cricoid ring</td>
</tr>
<tr>
<td>Compliant chest wall28</td>
<td>Thoracic skeleton in children is primarily cartilaginous which leads to increase compliance; intrinsic muscle tone is required to maintain lung volumes and prevent chest wall distortion</td>
<td>Increased risk of respiratory muscle fatigue, atelectasis, and respiratory failure</td>
</tr>
</tbody>
</table>

Appendix B

Table 13: Physiological considerations in pediatric patients29-39

<table>
<thead>
<tr>
<th>Physiologic Feature</th>
<th>Result</th>
<th>Influence on Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-related respiratory rate29</td>
<td>Normal vital signs vary by age; variations in breathing patterns occur</td>
<td>Discriminating normal from concerning vital signs is essential in assessing respiratory status and response to therapy</td>
</tr>
<tr>
<td>Preferential nasal breathing30-33</td>
<td>Infants are obligate nasal breathers</td>
<td>Obstruction by secretions, edema, or compression from non-flowing nasal cannula can lead to increased work of breathing</td>
</tr>
<tr>
<td>Lower functional residual capacity34-37</td>
<td>Young children have minimal intrapulmonary oxygen stores to use during periods of hypoventilation or apnea</td>
<td>Increased need for pre-oxygenation and possible bag-mask ventilation</td>
</tr>
</tbody>
</table>
**Higher oxygen metabolism**\(^{36,38,39}\) Infants consume \(\text{O}_2\) twice as fast as adults which results in shorter tolerance of apnea

**Time to oxygen desaturation increases with age**

**Prone to respiratory fatigue**\(^{38}\) Infants and young children have less slow-twitch fibers in intercostal muscles

**More prone to fatigue and respiratory failure**

**Higher vagal tone** Pronounced vagal response to laryngoscopy and airway suctioning

**Potentiates risk for bradycardia during RSI**

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**Appendix C**

**Table 13: Trial summaries of pediatric etomidate use\(^{66-69}\)**

<table>
<thead>
<tr>
<th>Procedural Sedation</th>
<th>Authors</th>
<th>Design</th>
<th>n</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Di Liddo et al.(^{66}) (2006)</td>
<td>RCT</td>
<td>100</td>
<td>Etomidate group achieved adequate sedation more than midazolam group (92% vs. 36%) Induction and recovery times were higher in etomidate group</td>
</tr>
<tr>
<td></td>
<td>Lee-Jayaram et al.(^{67}) (2010)</td>
<td>Prospective</td>
<td>23</td>
<td>Etomidate/fentanyl had ↓ sedation and recovery times compared to ketamine/midazolam Ketamine/midazolam had lower pain/distress scores compared to etomidate/fentanyl group</td>
</tr>
<tr>
<td></td>
<td>Mandt et al.(^{68}) (2012)</td>
<td>Prospective</td>
<td>60</td>
<td>Etomidate (0.2 mg/kg) + fentanyl (1 mcg/kg) provided successful initial sedation in 39/60 (65%) patients &amp; 59/60 (98.35) with an additional dose of etomidate (0.1 mg.kg)</td>
</tr>
<tr>
<td></td>
<td>Ma et al.(^{59}) (2015)</td>
<td>RCT</td>
<td>60</td>
<td>BP &amp; HR significantly ↓ with etomidate vs. propofol Respiratory depression, bradycardia, hypotension, &amp; pain on injection significantly ↑ with propofol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance anesthesia</th>
<th>Authors</th>
<th>Design</th>
<th>n</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doom et al.(^{70}) (1976)</td>
<td>Prospective</td>
<td>80</td>
<td>No adverse effects reported with intermittent bolus etomidate use and emergence time was shorter than methohexitone</td>
</tr>
</tbody>
</table>

References: