Etomidate Use in Septic Shock: A Lively Debate or a Killer Controversy?

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Learning Objectives:
1. Describe the physiological role of cortisol
2. Understand the pathophysiology of corticosteroid insufficiency in critically ill patients
3. Evaluate the impact of etomidate-induced adrenal suppression in the septic patient population
4. Identify the clinical significance of a single-dose of etomidate for use as an induction agent
THE ROLE OF CORTISOL

I. Cortisol function
   a. Mediator of stress response
      i. Metabolic
         1. Increase hepatic gluconeogenesis
         2. Inhibit adipose tissue uptake of glucose
      ii. Cardiovascular
         1. Increase vascular smooth muscle sensitivity to catecholamines
         2. Decrease production of nitric oxide restoring responsiveness to blood pressure
      iii. Anti-inflammatory
         1. Suppress immune activation of circulating leukocytes
         2. Inhibit production of excessive cytokine release

II. Hypothalamic-pituitary-adrenal (HPA) axis
   a. Primary function is to maintain basal and stress-related homeostasis
      i. Mediates stress response synergistically with the sympathoadrenal system
      ii. Stimulated via three cytokines: Tumor necrosis factor α (TNF α), Interleukin-1 (IL-1) and Interleukin-6 (IL-6)
   b. Main output is cortisol as a result of stressful stimuli
      i. Hypothalamus secretes corticotropin releasing hormone (CRH)
      ii. CRH stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary
      iii. ACTH stimulates the release of cortisol from the adrenal cortex
         1. Regulated through negative feedback mechanisms
            a. Cortisol production
            b. CRH-neutralizing antibodies
            c. Prostanoid-synthesis inhibitors
III. Cortisol physiology
   a. Major endogenous glucocorticoid\textsuperscript{4,5}
      i. Adrenal gland does not store cortisol
      ii. Produced upon demand as a result of stressful stimuli
   b. Cholesterol conversion to pregnenolone\textsuperscript{7}
      i. Principal precursor
      ii. 80\% of circulating cortisol is derived from plasma cholesterol
   c. Less than 10\% exists as free cortisol in plasma\textsuperscript{4,5,8,9}
      i. Free cortisol is biologically active
      ii. Remaining 90\% of circulating cortisol is bound to corticosteroid binding globulin (CBG)

IV. Cortisol production
   b. Synthesized within the zona fasciculata of the adrenal cortex\textsuperscript{10}
      i. Secreted in pulses in a diurnal pattern\textsuperscript{7}
         1. Peak levels seen between 0400 and 0800\textsuperscript{11}
            a. Levels vary between 6-23 mcg/dL
         2. Levels are the lowest around midnight
            a. Levels vary between 3-16 mcg/dL
   c. Response to acute illness\textsuperscript{4,5}
      i. CBG levels falls by as much as 50\%
         1. Percentage of circulating free cortisol increases
         2. The half-life of cortisol varies from 70-120 minutes\textsuperscript{11,12}
      ii. Loss of original diurnal rhythm\textsuperscript{8}
         1. The level of circulating cortisol is directly related to the severity and duration of illness
         2. Levels > 25 mcg/dL represent an adequate response\textsuperscript{13}
ADRENAL INSUFFICIENCY IN SEPSIS

V. Critical illness-related corticosteroid insufficiency (CIRCI)
   a. Incidence
      i. 10-20% in critically ill medical patients
      ii. As high as 60% in severe sepsis and septic shock
   b. Definition
      i. Inadequate corticosteroid activity for the severity of the illness
      ii. Usually a reversible condition caused by pro-inflammatory mediators
      iii. Secondary to insufficient corticosteroid mediated down-regulation of inflammatory transcription factors
   c. Clinical features
      i. Adrenergic receptors are down-regulated
      ii. Vascular smooth muscle hyporesponsiveness and myocardial depression
         1. Hypotension refractory to fluids
         2. Requirement of vasopressors
   d. Diagnosis
      i. Random total serum cortisol level (“stress” cortisol level)
      ii. Delta cortisol
         1. Change in serum cortisol in response to 250 mcg of synthetic ACTH
         2. Measures the ability of the adrenal gland to increase cortisol production in response to ACTH
         3. High specificity in CIRCI diagnosis
      iii. No true consensus on values
         1. Random total cortisol < 10 mcg/dL is considered low
         2. Delta cortisol of < 9 mcg/dL post cosyntropin stimulation test
         3. Random cortisol level < 18 mcg/dL considered inappropriately low in patients with shock
   e. Etiology
      i. Abnormal functioning of the HPA axis results in decreased production of CRH, ACTH, and cortisol
      ii. Structural damage to the adrenal gland
         1. Hemorrhage due to underlying coagulopathy
         2. Infarct resulting from refractory hypotension
      iii. Corticosteroid tissue resistance
         1. Failure to down-regulate inflammatory cytokines due to impaired glucocorticoid receptor activity
         2. TNF α and IL-1 have been shown to inhibit the action of ACTH
   iv. Impaired availability of HDL-cholesterol
      1. Diminished activity of steroidogenic enzymes
      2. Shown to be reduced in critically ill patients
      3. Low HDL levels are associated with an attenuated response to cosyntropin
   v. Various disease states and medications (see Appendix A)
vi. Limitations \(^\text{4,5}\)

1. Cortisol assays measure the total hormone concentration rather than the biologically active form
   a. The active form is responsible for the physiological function of the hormone
2. Significant variation in assay characteristics
   a. Specificity, sensitivity, and performance are not uniform
   b. Variations are substantial in septic shock patients
      i. Increase in cross-reactivity of the assay with precursors or metabolites of cortisol that accumulate in sepsis
3. Delta cortisol
   a. Does not assess the integrity of the HPA axis, response of HPA axis to other stressors, or adequacy of stress cortisol levels
   b. Poor reproducibility of the ACTH stimulation test in critically ill patients

VI. CIRCI in Sepsis \(^\text{3,5}\)

a. Increased incidence over critically ill non-septic patients
   i. Related to the increased presence of pro and anti-inflammatory cytokines
b. HPA axis and immune system are closely integrated
   i. Cortisol acts to suppress
      1. Immune activation of circulating leukocytes
      2. Pro-inflammatory cytokines
   ii. Inadequate response of cortisol to inflammation \(^\text{23,24}\)
      1. Increased susceptibility to infection
      2. Progression and worsening of sepsis
 c. Shift toward anti-inflammatory immunosuppressive state
   i. Overstimulation of immune system
   ii. Inadequate levels of cortisol unable to maintain cytokine balance
   iii. Cytokine storm and death

VII. Septic shock \(^\text{18,19}\)

a. Definition
   i. Sepsis associated with circulatory failure characterized by persistent arterial hypotension despite adequate fluid resuscitation
b. Pathophysiology
   i. Innate immune response to microorganism-associated molecular patterns (MAMPs) is deregulated
   ii. Imbalanced cytokine response
      1. Responses that are normally beneficial for fighting infection are converted into excessive damaging inflammation
   iii. Failure of the vascular smooth muscles to constrict
      1. Impaired tissue oxygenation
   iv. Results in widespread inflammation, organ damage and death
 c. Stabilization
   i. Airway management is often a necessity in these critically ill patients
   ii. Protection of the airway helps maintain ventilation and oxygenation
VIII. Rapid Sequence Intubation (RSI)\textsuperscript{25,26-31}
   a. Developed to assist health care professionals in the placement of emergent artificial airways for patients requiring assisted ventilation
   b. Seven step process used to ensure each patient receives rapid airway placement in a universally concise manner
      i. Allows for intubation with a decreased risk of vomiting and aspiration
   c. Administration of a sedative (induction agent) followed by a neuromuscular blocking agent to facilitate endotracheal intubation (see Appendix B)
   d. Results in an intubation success rate of greater than 98%

IX. RSI Procedure\textsuperscript{28}

**Figure 2. Timeline of rapid sequence intubation**

\begin{figure}
\centering
\includegraphics[width=\textwidth]{timeline.png}
\caption{Timeline of rapid sequence intubation}
\end{figure}
X. Role of Etomidate\textsuperscript{27,28}

a. Serves as the gold standard for induction in RSI
   i. Used in nearly 70% of all RSI procedures according to the National Emergency Airway Registry
   ii. Induction agents are used to facilitate intubation by rapidly inducing unconsciousness

b. Mechanism of action\textsuperscript{26,29}
   i. Ultrashort-acting nonbarbiturate hypnotic agent
   ii. Acts on the CNS to stimulate gamma-aminobutyric acid (GABA) receptors and depress the reticular activating system

c. Pharmacokinetic parameters\textsuperscript{29}
   i. Standard induction dose is 0.3 mg/kg
   ii. Hemodynamically unstable dose is 0.15 mg/kg
   iii. Onset of action is 5-15 seconds\textsuperscript{27,30}
      1. Reaches peak brain concentrations within one minute of IV infusion
      2. Induces sleep within 30 seconds of administration
   iv. Duration of action is 5-15 minutes
      1. Elimination half-life in 2.6-3.5 hours
      2. Shorter clinical hypnotic effect due to rapid redistribution from the brain to inactive tissues

d. Favorable side effect profile
   i. Hemodynamically neutral\textsuperscript{20}
      1. Decreased risk of hypotension compared to alternative agents
         a. Midazolam and propofol can decrease mean arterial pressure by 10-20%
         b. Critically ill patients with hypotension are at risk of developing severe life-threatening complications at induction\textsuperscript{31,32}
      2. Lack of cardiac and respiratory adverse effects\textsuperscript{20,33}
         a. Minimal effect on cardiac output and myocardial oxygenation
            i. Maintains cardiac blood flow
         b. Limited ventilation suppression due to lack of histamine release
         c. Appealing option in sepsis patients who have limited hemodynamic reserve\textsuperscript{25}
            i. Cardiovascular instability is a major cause of morbidity and mortality
   ii. Neuroprotective effects\textsuperscript{20,33}
      1. Reduces intracranial pressure by lowering cerebral blood flow and oxygen consumption
      2. Advantageous in trauma patients with head injuries
      3. Maintains cerebral perfusion pressure\textsuperscript{21,31}
XI. From the beginning\textsuperscript{21,36}
   a. 1972
      i. Etomidate first introduced into clinical practice in Europe
      ii. Initially used for the maintenance of sedation in the operating room and the intensive care unit
   b. 1983
      i. Approved for use in the United States\textsuperscript{57,38}
      ii. Promoted as a safe agent for continuous sedation in mechanically ventilated patients
      iii. Preliminary reports of increased fatalities related to etomidate infusion in multi-trauma patients\textsuperscript{36}
         1. Ledingham and Watt, in Glasgow, noticed mortality rates rose from 25 to 44%
            a. When the predominant means of sedation was changed from benzodiazepine agents to etomidate
   c. 1984
      i. Watt and Ledingham published a retrospective review in \textit{Anaesthesia}\textsuperscript{39}
         1. Adrenal insufficiency was found to be the direct consequence of etomidate therapy
         2. Mortality rate was further increased when patients were classified according to duration of ventilation and means of sedation
            a. Benzodiazepine agents, 28\% versus etomidate, 77\%; \( p< 0.0005 \)
      ii. Establishment of the detrimental effects of etomidate as a long-term anesthetic and sedative\textsuperscript{40}
   d. 2002
      i. Debate reopened
      ii. Controversy arose regarding a single bolus dose of etomidate
         1. Annane et al. highlighted the lack of cortisol response to exogenous ACTH in patients who received etomidate\textsuperscript{41}
      iii. Reports of increased incidence of relative adrenal suppression in the critically ill
XII. Etomidate and adrenal suppression\textsuperscript{21,42}
   a. Limits the endogenous stress response important in septic patients
   b. Transiently inhibits the conversion of cholesterol to cortisol
      i. Reversible and dose-dependent blockade of 11 \( \beta \)-hydroxylase
         1. Prevents the increase in cortisol secretion in response to ACTH
         2. Relatively minor effect on 17 \( \alpha \)-hydroxylase
   c. Limited effect on aldosterone inhibition
      i. Renin and angiotensin are the strongest stimulators for aldosterone release
      ii. Lack of a negative feedback mechanism
   d. Rise in ACTH levels seen in patients who receive etomidate indicate a lack of response by the adrenal cortex to endogenous ACTH stimulation

Figure 2. Mechanism of Etomidate-Induced Adrenal Suppression

\[ \text{Cholesterol} \]
\[ \text{Pregnenolone} \]
\[ \text{17\( \alpha \)-hydroxypregnenolone} \]
\[ \text{17\( \alpha \)-hydroxyprogrenolone} \]
\[ \text{17\( \alpha \)-hydroxyprogesterone} \]
\[ \text{Progesterone} \]
\[ \downarrow \text{Cortisol} \]
\[ \downarrow \text{Corticoesterone} \]
\[ \downarrow \text{Aldosterone} \]

\[ \text{ETOMIDATE} \]
THE ETOMIDATE DEBATE

XIII. Controversy surrounding etomidate

a. Effect of etomidate on adrenal insufficiency
   i. Annane et al. reported low dose hydrocortisone and fludrocortisone reduced the risk of death in patients with septic shock.41
      1. 68 out of 72 (94%) patients who received etomidate had relative adrenal insufficiency compared to 71% of those who did not receive etomidate
   ii. Mohammad et al. retrospectively analyzed 152 patients with septic shock who had a cosyntropin stimulation test.44
      1. 76% of etomidate patients versus 51% of non-etomidate patients had relative adrenal insufficiency based on the delta cortisol levels
   iii. Cuthbertson et al. re-examined 96 patients with septic shock who received etomidate from the data collected in the CORTICUS study.45
      1. 61% developed adrenal insufficiency compared to 44.6% in the etomidate free patient population

b. Etomidate and vasopressor support
   i. Dmello et al. retrospective analysis of 113 etomidate treated patients with severe sepsis and septic shock.46
      1. Failed to show a significant difference in vasopressor use, p=0.314
   ii. Ray and McKeown conducted a retrospective review of 159 septic shock patients.47
      1. No difference seen in vasopressor use, maximum dose, or duration of therapy
   iii. Annane et al. reported in a correspondence that etomidate-treated patients required a greater amount of vasopressors the day following etomidate administration.48
      1. Statistically significant difference, p<0.001

c. Impact on mortality
   i. Dmello et al.46
      1. Multivariate analysis demonstrated no significant association of etomidate with mortality, p=0.78
   ii. Ray and McKeown47
      1. No statistical differences seen in hospital mortality, p=0.23
         a. Lower doses were administered 0.1-0.3 mg/kg
   iii. Cuthbertson et al.45
      1. Increase in mortality rates seen
         a. 42.7% in the etomidate group vs. 30.5% in the non-etomidate group
         b. Univariate analysis found statistical significance, p=0.02
         c. Adjustment for confounders
            i. Multivariate analysis did not result in statistical significance, p=0.06
         d. Adjustment for severity of illness
            i. Multivariate analysis resulted in statistical significance, p=0.03
**REVIEW**

XIV.  Review  
   a.  It is reasonable to conclude that a single dose of etomidate increases the likelihood a patient with sepsis will have an attenuated response to exogenous cosyntropin\(^{41,44-48}\)
   b.  Mortality rates  
      i.  Increase in mortality rates seen in a priori sub-study resulted in one out of two multiple regression models showing statistical significance\(^{45}\)
      ii.  No association seen between mortality and etomidate in various other studies
      iii.  Lower doses of etomidate may contribute to the lack of association
   c.  Vasopressor support  
      i.  Increased need in etomidate treated patients has been documented from data collected in only one study to date\(^{41}\)
      ii.  The majority of studies published have not seen a correlation in etomidate use and increased vasopressor support
      iii.  Favorable safety profile ensures predictable hemodynamic stability upon induction

**CLINICAL QUESTIONS**

XV.  What is the clinical significance of adrenal insufficiency associated with single-dose etomidate?

XVI.  Important considerations  
   a.  Does etomidate worsen clinical manifestations of CIRCI in the septic population?  
      i.  Hospital length of stay
      ii.  Duration of mechanical ventilation
      iii.  Increased vasopressor support
   b.  Are there safer induction agents available for use in RSI?
   c.  Is etomidate associated with an increased risk of mortality in sepsis patients?

XVII.  Preview of literature review

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jabre P, et al</td>
<td>Etomidate vs. ketamine</td>
<td>Ketamine is a safe alternative in RSI</td>
</tr>
<tr>
<td>Tekwani K, et al</td>
<td>Etomidate vs. midazolam</td>
<td>No difference seen in length of stay</td>
</tr>
<tr>
<td>McPhee C, et al</td>
<td>Etomidate</td>
<td>No association with increased mortality</td>
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</tbody>
</table>

**Objective**
To determine if ketamine is a safe and valuable alternative to etomidate for endotracheal intubation in critically ill patients.

**Design**
- Prospective, randomized, controlled, single-blind trial
- 12 emergency departments and 65 intensive care units (ICU) in France

**Patient Population**
- **Inclusion:** ≥ 18 yr requiring sedation for emergency intubation
- **Exclusion:** cardiac arrest, contraindications to succinylcholine, ketamine or etomidate, known pregnancy, patients discharged alive from the ICU within 3 days, patients who died prior to reaching the hospital
- Diagnosis of sepsis: 76/469 (16%)

**Outcomes**
- **Primary:**
  - The maximum sequential organ failure assessment (SOFA) score during the first three days in the intensive care unit
- **Secondary:**
  - 28-day all-cause mortality, Δ-SOFA score, days free from ICU, organ support-free days
- **Subgroup analysis:**
  - Septic and trauma patients
  - SOFA<sub>max</sub>
  - 28-day mortality rate

**Methods**
- **Rapid sequence intubation agents used:**
  - Patients randomized and assigned to one of two arms
    - Etomidate 0.3 mg/kg
    - Ketamine 2 mg/kg
  - Succinylcholine 1 mg/kg was given immediately after the sedative
  - Continuous sedation was initiated with either midazolam 0.1 mg/kg/h combined with fentanyl 2-5 mcg/kg/h or sufentanil 0.2-0.5 mcg/kg/h
  - Assessed organ dysfunction and failure occurring after admission to the intensive care unit using the SOFA score
  - Adrenal insufficiency defined as
    - Random cortisol concentration < 276 nmol/L (10 mcg/dL) or a difference from baseline concentration of < 250 nmol/L (9 mcg/dL) at 30 or 60 minutes after ACTH stimulation test
  - Non-responder defined as
    - Increase in cortisol did not exceed 250 nmol/L (9 mcg/dL) at 30 or 60 minutes after the ACTH stimulation test
  - Safety: Intubation difficulty, arterial blood pressure, oxygen saturation, cardiac arrest

**Results**
- **Primary and secondary outcomes**
- 469 patients were enrolled-baseline characteristics similar between groups
  - Etomidate group, n=234
  - Ketamine group, n=235

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Etomidate</th>
<th>Ketamine</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>28-day mortality (n[%,95% CI])</td>
<td>81 (35%,29 to 41)</td>
<td>72 (31%,25 to 37)</td>
<td>0.36</td>
</tr>
<tr>
<td>Δ SOFA (median [IQR])</td>
<td>1.5 (0 to 3)</td>
<td>1 (0 to 3)</td>
<td>0.20</td>
</tr>
<tr>
<td>ICU-free days (median [IQR])</td>
<td>4 (0 to 22)</td>
<td>6 (0 to 23)</td>
<td>0.57</td>
</tr>
<tr>
<td>Organ support free days (median [IQR])</td>
<td>Mechanical ventilation</td>
<td>12 (0 to 25)</td>
<td>15 (0 to 26)</td>
</tr>
<tr>
<td></td>
<td>Vasopressors</td>
<td>27 (14 to 28)</td>
<td>28 (20 to 28)</td>
</tr>
<tr>
<td>SOFA&lt;sub&gt;max&lt;/sub&gt; score (mean [SD])</td>
<td>10.3 (3.7)</td>
<td>9.6 (3.9)</td>
<td>0.056</td>
</tr>
</tbody>
</table>
Results

- Subgroup analysis
  - Etomidate group, n=41; ketamine group, n=35

<table>
<thead>
<tr>
<th>Variable</th>
<th>Etomidate (mean [SD])</th>
<th>Ketamine (mean [SD])</th>
<th>Absolute difference of SOFA_max (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA_max</td>
<td>12.4 (3.8)</td>
<td>10.8 (4.5)</td>
<td>1.6 (-0.3 to 3.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Etomidate (no. deaths/total no. patients)</th>
<th>Ketamine (no. deaths/total no. patients)</th>
<th>Odds ratio of death at day 28 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rate</td>
<td>17/41 (41%)</td>
<td>12/35 (34%)</td>
<td>1.4 (0.5 to 3.5)</td>
</tr>
</tbody>
</table>

- Trauma patients 104/469 (22%)
  - 28 day-mortality rate: Etomidate (26%) vs. ketamine (30%)

- The percentage of non-responders to the ACTH hormone stimulation test was significantly higher in the etomidate group, p <0.0001
- Median cortisol levels were significantly depressed in the etomidate group compared with ketamine (16 vs 25 mcg/dL; p < 0.0001) at a median of 7 hours post-induction
- Mortality did not differ significantly between the non-responders and responders (44/142 [31%, 95% CI 23-39] vs 19/90 [21%, 13-29]; p= 0.11)
- Safety
  - No statistical difference in difficulty of intubation or early complications after intubation

Author's Conclusion

- The percentage of patients with adrenal insufficiency was significantly higher in the etomidate group than in the ketamine group
- A single etomidate bolus is not associated with a significant increase in morbidity or mortality compared with ketamine in patients admitted to the intensive care unit
- Ketamine is a safe and valuable alternative to etomidate for endotracheal intubation in critically ill patients

Critique

- Only 76/469 (16%) of the study population had a final diagnosis of sepsis
- Failure to enroll a larger number of patients with sepsis could have led to a type II error
- The subgroup analyses were not adequately powered to detect differences in early and 28-day mortality
- A further study focusing solely on sepsis patients is warranted

<table>
<thead>
<tr>
<th>Objective</th>
<th>To determine whether etomidate use to facilitate intubation in the ED of patients with suspected sepsis is associated with prolonged length-of-stay (LOS) compared to midazolam</th>
</tr>
</thead>
</table>
| Design    | • Prospective, randomized, double-blind trial  
• Study occurred over an 18-month period (November 2007 – May 2009)  
• Intention-to-treat (ITT) and per-protocol analyses of confirmed sepsis patients conducted |
| Patient Population | • Inclusion: ≥ 18 years, intubated in the ED, suspected infectious cause for their illness  
• Exclusion: Pregnancy, cardiopulmonary arrest before arrival in ED, do-not-resuscitate status  
• Diagnosis of sepsis: 96/120 (80%) |
| Outcomes  | • Primary: Hospital LOS  
• Secondary: In-hospital mortality, ICU LOS, Length of time intubated |
| Methods   | • Rapid sequence intubation agent used: Etomidate 0.3 mg/kg vs. midazolam 0.1 mg/kg  
• Blinding:  
  o Identical study vials of etomidate or midazolam were prepared by pharmacy and stored in kits  
  o Kits were labeled with numbers that reflected the assignment generated by a randomization sequence generator and placed in an automated medication dispensing cabinet  
• Measurements:  
  o Severity of illness was determined by  
    ▪ Simplified Acute Physiology II (SAPSII) score  
    ▪ Sequential Organ Failure Assessment (SOFA) score  
    ▪ Mortality in Emergency Department Sepsis (MEDS) score  
  • Safety:  
    o Pulse oximetry and systolic blood pressure values were similar in both treatment groups before and after intubation |
| Results   | • 120 patients enrolled |

| Intention-to-Treat Population |  |
|-------------------------------|-------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Outcome                      | Midazolam N=59               | Etomidate N=61  | Difference (95% CI) | P value         |
| Primary Hospital LOS, days   | 9.5 (4.6 to 15.7)            | 7.3 (3.1 to 12.9) | 2.2 (-0.7 to 4.8) | 0.17            |
| Secondary ICU LOS, days      | 4.2 (2.2 to 6.9)             | 3.1 (1.9 to 5.6) | 1.1 (-0.3 to 1.8) |                 |
| Ventilator days              | 2.8 (1.5 to 5.5)             | 2.1 (1.3 to 4.1) | 0.7 (-0.3 to 1.5) |                 |
| In-hospital mortality No.,% (95% CI) | 21 (36, 24 to 49) | 26 (43, 30 to 56) | 7% (-10% to 24%) |                 |

• Kaplan-Meier survival analysis showed no statistically significant difference between groups for in-hospital mortality (p=0.22)  
• Safety parameters:  
  o Systolic blood pressure change postintubation  
    ▪ Midazolam: 16 mmHg  
    ▪ Etomidate: 7 mmHg  
  o 25% of patients in both groups developed a SBP less than 90 mmHg after intubation
**Results**

- Per-protocol analysis
  - Confirmed septic patients (N=96)
  - Confirmed septic shock (N=51)

<table>
<thead>
<tr>
<th>Per-Protocol Population</th>
<th>Midazolam N=51</th>
<th>Etomidate N=45</th>
<th>Difference (95% CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
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<tr>
<td>Hospital LOS, days</td>
<td>10.2 (6.7 to 18)</td>
<td>9.2 (4.5 to 12.9)</td>
<td>1.0 (-0.1 to 5.9)</td>
<td>0.06</td>
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<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ICU LOS, days</td>
<td>4.2 (2.6 to 6.8)</td>
<td>3.4 (2.2 to 5.7)</td>
<td>0.8 (-0.5 to 1.8)</td>
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<tr>
<td>Ventilator days</td>
<td>2.8 (1.6 to 5.3)</td>
<td>2.3 (1.5 to 4.4)</td>
<td>0.5 (-0.5 to 1.4)</td>
<td></td>
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<tr>
<td>In-hospital mortality No. (%, 95% CI)</td>
<td>17 (33, 21 to 48)</td>
<td>19 (42, 28 to 58)</td>
<td>9% (-10% to 27%)</td>
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</table>

**Author’s Conclusion**

- There seems to be no significant difference in hospital LOS between sepsis suspected patients who received etomidate and those who received midazolam when intubated in the ED
- No significant differences between groups was detected in secondary outcomes, though proportionally more deaths in the etomidate group
- Per-protocol sub-group analysis also found no significant differences between effects of midazolam and etomidate in selected patients

**Critique**

- The use of unknown adjunctive therapies may have been a contributed to erroneous outcomes
- Subsequent uses of etomidate throughout patient’s hospitalization were not monitored
- The study was underpowered to detect differences in secondary outcomes
<table>
<thead>
<tr>
<th>Objective</th>
<th>To determine if single-dose etomidate was associated with increased in-hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Retrospective cohort study evaluating the safety of etomidate for ICU intubation in sepsis, severe sepsis, or septic shock</td>
</tr>
</tbody>
</table>
| Patient Population | Inclusion: > 18 yr, intubated within the ICU, septic at the time of intubation  
Exclusion: Incomplete medication or clinical records, intubated outside ICU, previous etomidate administration, evidence of multiple intubations  
Studied sepsis, severe sepsis, and septic shock patients  
Diagnosis of septic shock: 650/2014 (32%) |
| Outcomes | Primary:  
In-hospital mortality in septic patients  
Secondary:  
ICU mortality, hospital and ICU length of stay (LOS), days of mechanical ventilation, days of vasopressor use in severe sepsis and septic shock |
| Methods | Data collected from Philips eICU Research Institute ICU clinical database  
Extensive dataset of critically ill adult patients remotely monitored in tele-ICUs in the United States  
Patients included were intubated from 2008 through the third quarter of 2010 |
| Results | 2014 patients enrolled |

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Septic Patients (N=2014)</th>
<th>Etomidate (N=1102)</th>
<th>No Etomidate (N=912)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU mortality, n (%)</td>
<td>607 (30.1)</td>
<td>332 (30.1)</td>
<td>275 (30.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hospital LOS, median (IQR)</td>
<td>12.2 (6.3 to 20)</td>
<td>12.7 (6.8 to 20.2)</td>
<td>11.9 (6 to 19.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>ICU LOS, median (IQR)</td>
<td>6.4 (3.2 to 11.5)</td>
<td>6.4 (3.2 to 11.2)</td>
<td>6.5 (3 to 11.9)</td>
<td>0.88</td>
</tr>
<tr>
<td>Ventilator days, median (IQR)</td>
<td>4.1 (1.7 to 8.4)</td>
<td>4.1 (1.8 to 8)</td>
<td>4.1 (1.5 to 8.8)</td>
<td>0.82</td>
</tr>
<tr>
<td>Post-intubation vasopressor days, median (IQR)</td>
<td>2 (0 to 3)</td>
<td>2 (0 to 3)</td>
<td>2 (0 to 3)</td>
<td>0.61</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>755 (37.5)</td>
<td>410 (37.2)</td>
<td>345 (37.8)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

- In-hospital mortality regression analysis  
  - Higher risk of death associated with age, APACHE IV score, race, and certain comorbidities  
  - No association between etomidate and in-hospital mortality

- Septic shock alone (n=650)  
  - In-hospital mortality (95% CI): Etomidate (0.69-1.10)  
  - No statistically significant relationship or trend between etomidate and in-hospital mortality

**Author’s Conclusion**  
Overall in-hospital mortality was not associated with etomidate use  
No statistical significance seen in vasopressor use, duration of mechanical ventilation, ICU LOS, or hospital LOS  
In the sickest subset group, septic shock, etomidate was not associated with increased mortality  
In-hospital mortality was adequately powered

**Critique**  
- Retrospective evaluation provides potential weaknesses as some patients may have been misclassified  
- Limited generalizability to patients in different settings  
- The lack of adrenal axis evaluation limits the correlation of adrenal function to outcomes measured  
- A primary outcome measure of 28-day mortality would have been superior to in-hospital mortality
XX. Presenter’s conclusion
   a. Single-dose etomidate use in patients with sepsis has been proven to cause additive adrenal suppression\textsuperscript{41,44-48}
      i. The effects of this compounded suppression is still a controversial debate
      ii. The transient adrenal suppression is dose-related
   b. Etomidate use should not be abandoned in patients with severe sepsis or septic shock
      i. Single-dose etomidate does not increase the risk of hospital mortality in septic patients
      ii. Currently only hemodynamically neutral induction agent available
   c. Increased awareness of alternative agents
      i. Ketamine appears to be safe and effective alternative agent\textsuperscript{49}
         1. Appropriate option in hemodynamically unstable patients
         2. Careful consideration is warranted in cardiovascular disease or TBI patients
   d. Clinical equipoise maintained
      i. Detrimental effects of etomidate-induced cortisol inhibition on clinical outcomes is not substantiated by current literature
      ii. Without adequately powered prospective trials to accurately assess the clinical significance of single-dose etomidate, one cannot confidently choose to abandon the use of a drug whose benefit seems to outweigh its risk


REFERENCES


APPENDICES

Appendix A. Causes of Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Disease states</th>
<th>Primary adrenal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis/Systemic inflammatory response syndrome</td>
<td></td>
</tr>
<tr>
<td>Metastatic carcinoma to the lung, brain or kidney</td>
<td></td>
</tr>
<tr>
<td>Systemic fungal infections</td>
<td></td>
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<tr>
<td>Tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Acute hemorrhage/infarction</td>
<td></td>
</tr>
<tr>
<td>Autoimmune adrenalitis</td>
<td></td>
</tr>
<tr>
<td>HIV infections</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Etomidate</td>
<td></td>
</tr>
<tr>
<td>Metyrapone</td>
<td></td>
</tr>
<tr>
<td>Mitotane</td>
<td></td>
</tr>
<tr>
<td>Rifampin (increased cortisol metabolism)</td>
<td></td>
</tr>
<tr>
<td>Phenytoin (increased cortisol metabolism)</td>
<td></td>
</tr>
</tbody>
</table>

Secondary adrenal insufficiency

<table>
<thead>
<tr>
<th>Disease states</th>
<th>Secondary adrenal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary or metastatic tumor</td>
<td></td>
</tr>
<tr>
<td>Empty-sella syndrome</td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis, histiocytosis</td>
<td></td>
</tr>
<tr>
<td>Postpartum pituitary necrosis</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Megesterol acetate</td>
<td></td>
</tr>
</tbody>
</table>

Appendix B. Additional agents used for induction in RSI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Benefits</th>
<th>Cautions</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0.2-0.3 mg/kg</td>
<td>Anticonvulsant, muscle relaxant, amnestic effects, rapid onset</td>
<td>Hypovolemia, traumatic brain injury (TBI)</td>
<td>Tachycardia, hypotension, respiratory depression, wide-dose response</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1.5 mg/kg</td>
<td>Preservation of pharyngeal reflexes, relaxes bronchial smooth muscle</td>
<td>Intracranial pathology, acute coronary syndrome, hypertension</td>
<td>Increase in ICP, BP, HR, CO, and myocardial oxygen consumption, emergence reactions</td>
</tr>
<tr>
<td>Propofol</td>
<td>2 mg/kg</td>
<td>Decreased cerebral oxygen consumption and ICP, bronchodilator</td>
<td>Hemodynamically unstable patients, soy or egg allergies</td>
<td>Direct myocardial depression, drug-induced hypotension, reduction in cerebral perfusion pressure</td>
</tr>
</tbody>
</table>