Etomidate & Adrenal Dysfunction:
A Synthesis of the Evidence Regarding Etomidate In the Critically Ill

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ABSTRACT

Etomidate is often used in the intubation of critically ill and septic patients due to its lack of hemodynamic depression. This population, however, may be at greatest risk for complications of adrenal insufficiency due to use of etomidate. Research was explored on this topic to evaluate the safety of etomidate in this population, alternatives to etomidate, and the diagnosis and treatment of adrenal dysfunction in the critically ill. The synthesis of this research led to the development of a continuing education module to simplify this data for anesthesia providers.
PART 1: INTRODUCTION

Etomidate is an intravenous, nonbarbiturate, imidazole hypnotic agent commonly used to facilitate endotracheal intubation.\textsuperscript{1,2,3} Etomidate is considered a first-choice anesthetic agent in hemodynamically unstable patients due to its rapid onset, predictable effects, and relatively low cardiovascular compromise.\textsuperscript{2} It is known that etomidate, in continuous infusion or single dose, contributes to adrenal insufficiency in the critically ill patient.\textsuperscript{1,2,3,4,5,6} The Corticosteroid Therapy of Septic Shock (CORTICUS) study demonstrated that etomidate influenced adrenocorticotropic hormone (ACTH) test results and was significantly associated with negative outcomes.\textsuperscript{7} Other studies do not conclude a correlation between the use of etomidate and increased morbidity and mortality.\textsuperscript{8,9} Assertions have been made that the risk of adrenal insufficiency is slight and can be medically managed with exogenous steroids.\textsuperscript{8} Some have suggested that the adrenal dysfunction associated with etomidate may contribute to acute respiratory distress syndrome (ARDS)\textsuperscript{10} or that etomidate use should be abandoned entirely.\textsuperscript{11} Cotten and his colleagues assert that methoxycarbonyl-etomidate (MOC-etomidate), an etomidate analogue, has the desired effects of etomidate for induction of anesthesia, without the associated adrenal dysfunction.\textsuperscript{12,13} While many providers are aware that etomidate causes adrenal insufficiency, they may not know how that translates into their clinical practice. This review serves to compile available data to inform clinicians of current data and best practice.
PART 2: LITERATURE

LITERATURE SEARCH

A literature search was conducted to synthesize available research on adrenal insufficiency with etomidate use and explore the clinical implications of adrenal suppression. Google Scholar search engine was used for preliminary inquiry on the topic. MEDLINE, Cochrane Reviews, PubMed, and CINAHL were used as primary search databases. Search terms included etomidate and one of the following: adrenal, hemodynamic, shock, sepsis, and endotracheal intubation. The literature searches excluded articles published before the year 2000, articles not available in English, and pediatrics-oriented studies. With the exception of the research article regarding the in vitro study of MOC-etomidate, articles citing animal or in vitro studies alone were excluded. There was frequent overlap of the articles returned among search terms and databases. Thirty-nine articles met the search criteria and were included in this research synthesis. The focus of the articles used for data collection include etomidate versus other induction agents and the clinical impact, diagnosis, and treatment of adrenal suppression.

LITERATURE REVIEW

Levels of Evidence

The Joanna Briggs Institute rating system (See Appendix 5) was used to evaluate each article for level of evidence. The highest level of evidence is designated Level One, which is considered ready for implementation in clinical practice. Level One evidence is composed of a metasynthesis of research that includes well-designed randomly controlled trials and/or large experimental studies with narrow confidence intervals. Level Two evidence consists of small randomly controlled trials or experimental studies without randomization. Level Three evidence
can be either metasynthesis of text or opinion with credible synthesized findings, or a single high-quality research study. These studies may be cohort or observational studies with a control group or case-controlled research. Level Four evidence is expert opinion, consensus statements, or physiology bench research.

**Level One Evidence**

In 2007, Corticosteroid Therapy of Septic Shock (CORTICUS), a multicenter, retrospective, cohort study on cortisol levels as related to mortality in critical illness was published. Subjects from 20 European intensive care units were studied. Results showed that change in cortisol level after cosyntropin-stimulation were more predictive of outcomes than baseline cortisol levels. Etomidate was noted to negatively influence cosyntropin-stimulated increases in cortisol levels.

In 2010, Cohen and Venkatesh published a systematic review of evidence for the existence of relative adrenal insufficiency or critical illness associated corticosteroid insufficiency in septic patients. They deduce that absolute cortisol levels are not predictive of morbidity/mortality. Further, they suggest that routine testing of cortisol levels in the critically ill be abandoned unless future research demonstrates a positive correlation between corticoid blood levels and patient outcomes.

Jackson published a literature review in 2005 that concluded that there is a clinically significant decrease in steroidogenesis after single-dose etomidate for intubation. He states that further clinical trials are required to determine appropriateness of etomidate use in the critically ill.
In 2008, an international task force issued a consensus statement on the management of corticosteroid deficiency in critically ill adults. The task force made 12 evidence based recommendations for the treatment of septic and/or critically ill adults.

Mesotten evaluated research regarding the use of corticosteroid supplementation in the critically ill. He concludes that while early trials of supplemental steroids showed modest benefit, large-multicenter trials showed that supplemental steroids are possibly deleterious to patient outcomes. He asserts that patients should not be treated with supplemental steroids routinely, but rather as a rescue strategy when other treatments have failed.

Literature regarding the safety and efficacy of ketamine as an induction agent in the hemodynamically unstable was reviewed by Morris et al. The authors conclude that ketamine is a viable, and perhaps optimal, choice for induction of anesthesia in unstable patients. Eight of the 12 studies reviewed were in facilities considered “resource poor,” which indicates that they were located in third-world or war-torn regions without invasive monitoring and specialized equipment. End-point outcomes in these studies was either ease of intubation or survival. There is no data regarding the hemodynamic parameters during the use of ketamine, or effectively comparing it with other agents.

Cooper and Stewart conducted a systematic literature review in 2007 to identify the appropriate diagnostic and therapeutic strategies in adrenal insufficiency in the critically ill. The authors created an algorithm (Figure 1) to aid practitioners in determining whether steroid
supplementation would be beneficial. The dosing schedule they recommend as best practice is included as well.

**Figure 1: Diagnostic Algorithm**

Level Two Evidence

Absalom\(^{20}\) and colleagues conducted a randomized controlled trial comparing the effect of single-dose etomidate with a single dose of thiopentone in a group of critically ill patients. Cortisol assays were taken via blood sample from 35 patients. The assays were obtained prior to induction for baseline, and for a short ACTH stimulation test 24 hours postoperatively. The difference in peak cortisol values between the etomidate group and the control failed to reach statistical significance. However, etomidate was associated with a lower response to ACTH stimulation 24 hours postoperatively. The authors assert that this indicates an inhibition of the adrenal cortex after etomidate induction. The results of the study were published in 1999.

In 2002, Annane et al\(^ {21}\) published the results of a placebo-controlled, randomized, double-blind study comparing 28-day survival of septic patients with adrenal insufficiency. Adrenal
insufficiency was determined by response to a short corticotropin stimulation test. Non-responders to corticotropin were deemed to have adrenal insufficiency, whereas responders were assumed to have intact adrenocorticoid function. The 300 adult patients were divided into three groups, receiving either fludrocortisone, hydrocortisone, or a placebo. They concluded that seven-day treatment with hydrocortisone or fludrocortisone significantly reduced the risk of death without increasing adverse events.

Annane\textsuperscript{22} authored an editorial research review in 2005 regarding the use of etomidate to facilitate endotracheal intubation in the critically ill. He asserts that etomidate is an avoidable risk factor for the development of adrenal insufficiency in the critically ill patient. As such, etomidate use should be abandoned entirely in the intensive care unit. Evidence presented supports the conclusion that etomidate is associated with adrenal insufficiency, however no data is presented which directly links etomidate to worsened outcomes.

Annane and colleagues\textsuperscript{11} conducted an inception cohort study in 2006. The researchers sought to define and create diagnostic criterion for adrenal insufficiency in sepsis and critical illness. In healthy subjects, adrenal insufficiency is defined as a cosyntropin-stimulated cortisol level less than 18-20 mcg/dl. The authors concluded that septic patients with a baseline total cortisol level less than 10 mcg/dl or a cortisol increment less than 9 mcg/dl are very likely to have adrenal insufficiency. This article further asserts that patients with a cosyntropin stimulated increment of 9 mcg/dl or less had a hyporesponse to vasopressors and a significantly higher risk of death.
Methoxycarbonyl-etomidate (MOC-etomidate) was studied by Cotten et al\textsuperscript{13} in 2010. Animal trials of the drug suggest that MOC-etomidate, an analogue of etomidate, retains the favorable hemodynamic properties of etomidate, without causing adrenal suppression. Further studies will be needed to confirm that MOC-etomidate is safe and efficacious in humans.

Cotten et al\textsuperscript{3} conducted a retrospective registry study to identify risk factors associated with adrenal insufficiency in critically ill patients. They conclude that etomidate is the only modifiable risk factor significantly correlated with adrenal insufficiency, and that it should be avoided in the critically ill. They suggest alternative hypnotic agents, barbiturates and ketamine specifically, should be considered.

Cuthbertson\textsuperscript{4} and his associates conducted an a-priori substudy of the CORTICUS clinical trial. The endpoints evaluated were corticotropin response and 28-day mortality in patients who received etomidate. Of 499 analyzable subjects, 96 were administered etomidate. The authors conclude that the use of bolus-dose etomidate creates a statistically significant ($P = 0.03$) decrease in corticotropin response, and is likely associated with increased mortality. The authors advise that use of etomidate be avoided in patients deemed critically ill or in septic shock.

deJong\textsuperscript{5} et al conducted a retrospective study in the medical-surgical ICU of a major teaching facility. They found that one-quarter of patients with septic shock have concurrent adrenal insufficiency, regardless of etomidate use. In their subjects, use of etomidate for intubation did not contribute to mortality in multi-variate analysis.
Easby and Dodds\textsuperscript{23} conducted a literature review comparing different anesthetic agents used to facilitate endotracheal intubation in the prehospital setting. Their research uncovered no untoward effects of etomidate in the prehospital setting. The authors discuss the possibility of adrenal suppression caused by etomidate, stating that further research would be required to determine the sequela of etomidate’s adrenal effects. The factors the authors focused on were hemodynamic stability and ease of intubation with each agent.

Egan\textsuperscript{12} discussed the role of rapidly metabolized anesthetics such as MOC-etomidate in his 2009 editorial. He asserts that rapid onset and metabolism of new anesthetic agents will continue to improve the field of anesthesia.

Fellows\textsuperscript{24} et al conducted a small prospective study of six patients. Three received etomidate infusions for sedation, three did not. The etomidate group had significantly ($P = 0.05$) lower response to cortisol-stimulation testing and significantly higher ACTH levels than the control group. Published in 1983, this was one of the early studies to demonstrate that etomidate infusion was associated with adrenal dysfunction, though the specific mechanisms remained unclear.

Gwinnutt\textsuperscript{25} and his associates wrote an article outlining the best practice for anesthesia of trauma patients. They suggest use of etomidate for induction of general anesthesia in unstable trauma patients, citing its hemodynamic stability, reduction in brain oxygen demand and blood flow, and its lack of effect on intracranial pressure.
Hamrahian\textsuperscript{26} conducted a cohort study to evaluate the influence of cortisol-binding proteins on serum total cortisol and free cortisol concentrations during critical illness. Baseline serum cortisol, cosyntropin-stimulated cortisol, aldosterone, and free cortisol levels were measured in 33 healthy volunteers and 66 critically ill patients. They found that nearly 40\% of critically ill patients with hypoproteinemia had subnormal total serum cortisol levels, despite normal adrenal function. The authors suggest that measuring cortisol levels in the face of hypoproteinemia (albumin < 2.5g/dL) could lead to false diagnosis of adrenal dysfunction in the critically ill.

Etomidate use in rapid sequence induction (RSI) of the adult trauma patient was studied by Hildreth\textsuperscript{27} in a prospective randomly controlled trial. The trial included 30 participants, 18 received etomidate and succinylcholine, while the remaining 12 received fentanyl, midazolam, and succinylcholine. They found a statistically significant ($P < 0.001$) decrease in adrenocortical function in the group that received etomidate. Further, the etomidate group had increased duration of ventilator dependency ($P = 0.01$) and length of stay ($P = 0.05$).

A multicenter randomly controlled trial was conducted by Jabre\textsuperscript{9} and associates to compare the use of ketamine versus etomidate in RSI. Both drugs were paired with succinylcholine for RSI. The primary endpoint used in this study was the sequential organ failure assessment (SOFA) score. The SOFA score and ease of intubation did not differ significantly ($P = 0.056$) between the two groups. The percentage of patients with adrenal dysfunction was significantly higher in the etomidate group. The authors advocate use of ketamine for RSI of the hemodynamically compromised.
Lamberts\textsuperscript{28} reviewed literature regarding supplemental corticosteroids in severe illness. The article concludes that dysfunction of the hypothalamic-pituitary-adrenal axis can contribute to worsened outcomes after surgery, trauma, or severe illness. Evaluation of adrenal function via cosyntropin-stimulation tests and treatment of adrenal insufficiency with supplemental corticosteroids is recommended.

Mohammad\textsuperscript{29} and colleagues conducted a retrospective cohort comparison of adrenal insufficiency in septic patients who had received etomidate versus those who did not. The incidence of adrenal insufficiency, as evidenced by cosyntropin-stimulation test, was significantly higher in the patients who had received etomidate. The sample size of this study was relatively small, and further prospective cohort studies were recommended by the authors to confirm the results.

A retrospective cohort study was conducted to determine the effect of induction agent on vasopressor and steroid use in critically ill patients. Ray\textsuperscript{8} and his associates determined no significant differences in vasopressor, inotrope, or steroid use regardless of induction agent used. Vasopressor therapy was used less frequently and in smaller doses during induction in the group that received etomidate. Further, they found no difference in outcomes in patients who received steroid supplementation after etomidate use. They conclude that etomidate had no negative influence on ICU course or mortality.

Schenarts\textsuperscript{1} led a prospective, randomized, controlled trial of consecutive patients presenting to the emergency department who required intubation. Patients were intubated with either
etomidate or midazolam, in combination with succinylcholine. The resulting data shows that etomidate was associated with decreased adrenal response to cosyntropin-stimulation, but that serum cortisol levels remained within normal limits in both groups at four, 12, and 24 hours post induction.

Stoltenkamp\textsuperscript{30} compiled evidence from a number of studies for a lecture and accompanying pamphlet on etomidate and adrenal dysfunction. He states that no large prospective trial demonstrates increased mortality as a result of etomidate use. Several smaller studies fail to correlate etomidate with worsened outcomes or increased mortality.

Tekwani\textsuperscript{31} and colleagues collected non-randomized, prospective observational data from all patients meeting sepsis criteria who were intubated in the emergency department over a nine-month period. They found no significant increase in hospital length of stay or mortality (\(P = 0.08\)) in patients given etomidate for induction and intubation.

Vinclair\textsuperscript{32} and his associates conducted a prospective, observational cohort study to determine the incidence and duration of adrenal dysfunction after single dose etomidate. They found that 80\% of the non-septic patients who received etomidate demonstrated adrenal dysfunction. This dysfunction was correctable with supplemental steroids and reversed within 48 hours after dosing.

An early study of adrenal function after etomidate was conducted by Wagner and White\textsuperscript{6} in 1984. They show a clear correlation between etomidate and decreased adrenal response to
cosyntropin stimulation in patients who received either single dose or intravenous infusion of etomidate for routine surgery. The subjects in this study were healthy women of childbearing age, and none had negative outcomes regardless of etomidate use.

Warner\textsuperscript{10} and associates collected data from a prehospital hypertonic saline trial to evaluate for increased incidence of acute respiratory distress syndrome (ARDS) after induction with etomidate. Nonrandomized retrospective data was collected from a the trial, which included only trauma patients who were hypotensive in the prehospital setting. After controlling for confounding factors, they found an increased percentage of ARDS when etomidate was used for intubation, however, this data was not statistically significant. (P = 0.06).

**Level Three Evidence**

Lundy\textsuperscript{16} presents a case report of a 74 year old woman with adrenal insufficiency who required vasopressor and transvenous pacing after a single induction dose of etomidate. The authors provide a detailed review of the physiology of the adrenal response as well as a description of the 11\(\beta\) hydroxylase inhibition associated with etomidate use.

Mason\textsuperscript{33} and associates wrote a critique of the CORTICUS study. They assert that the study had limited power, noting that the study was terminated early with only 60\% of the planned number of subjects enrolled. They conclude that use of corticosteroid supplementation should be reserved for patients who are vasopressor dependent after adequate fluid resuscitation.

**Convergent Literature**
Research regarding etomidate and adrenal insufficiency has reached a consensus in several areas. First, etomidate is a hemodynamically stable hypnotic induction agent. Second, etomidate directly causes adrenal suppression which can decrease serum cortisol. Third, cortisol levels may influence morbidity and mortality in the critically ill.

Etomidate is an effective hypnotic agent which provides excellent hemodynamic stability during endotracheal intubation and induction of anesthesia. It is often used in the critically ill and hemodynamically unstable patients because of its lack of effect on hemodynamic parameters.\textsuperscript{23,25}

Unfortunately, etomidate is strongly associated with adrenal insufficiency and cortisol deficiency after use.\textsuperscript{1,2,3,4,5,6} Administration of etomidate inhibits the 11β-hydroxylase enzyme that converts 11-deoxycortisol into cortisol in the adrenal gland, leading to adrenal insufficiency.\textsuperscript{16,32,34} This inhibition is dose-dependent and reversible.\textsuperscript{30} Etomidate’s potency for inhibiting 11β-hydroxylase is 100 times greater than its hypnotic potency.\textsuperscript{13} The adrenal suppression of etomidate is limited to the adrenal cortex and has no impact on the production of catecholamines in the adrenal medulla.\textsuperscript{30}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{cortisol_synthesis.png}
\caption{Cortisol Synthesis Pathway}
\end{figure}
Evidence supports management of cortisol levels to within a defined range (15-34 mcg/dL) to optimize outcomes.\textsuperscript{2,16,21} Cortisol is integral in the maintenance of vascular tone and permeability as well as intravascular fluid volume.\textsuperscript{28} Acute adrenal insufficiency may result in syndromes resembling hypovolemic or hyperdynamic shock.\textsuperscript{28} Cortisol naturally rises in response to acute stressors, such as severe illness, trauma, and surgical stimulation.\textsuperscript{28} The use of etomidate in this patient population may blunt the normal increase in circulating cortisol, leading to a relative or absolute adrenal insufficiency.\textsuperscript{28} Adrenal insufficiency may be compounded by critical illness mediated corticosteroid resistance in the tissues.\textsuperscript{16}

**Divergent Literature**

Studies\textsuperscript{3,18} have also shown that ketamine is a viable choice for intubation of the critically ill, but there is conflict in the literature regarding whether ketamine is a superior induction agent in the hemodynamically unstable. Jabre\textsuperscript{9} and colleagues compared 28-day morbidity between single dose etomidate versus single dose ketamine. While a statistically significant ($P < 0.0001$) difference in cortisol levels was found between the two groups, there was not a difference in clinical outcomes.\textsuperscript{9} The study did show that ketamine was as effective as etomidate in the safe and efficacious intubation of hemodynamically unstable patients.\textsuperscript{9}

The impact that adrenal axis suppression has on morbidity and mortality is also heavily debated. Many\textsuperscript{20,22,24,27,29} have asserted that the inhibition of adrenal hormone synthesis could negatively impact survival and outcomes, however, none have been able to eliminate confounding factors.\textsuperscript{9} Other investigations\textsuperscript{1,8,9,31} have concluded that there are no significant ($P < 0.05$) differences in
outcomes based on the severity of adrenal dysfunction alone. Cohen\textsuperscript{15} suggests that responsiveness to ACTH is more strongly associated with increased morbidity and mortality than absolute cortisol levels. Similarly, Hamrahain\textsuperscript{26} writes that cortisol alone is not sufficient to diagnose adrenal dysfunction.

Conflicting evidence exists as to whether supplemental exogenous steroids are beneficial or harmful in the treatment of cortisol-deficient, critically-ill patients.\textsuperscript{5,8,15,17,20,21} High cortisol levels have been associated with increased risk of death in severe illness, as have inadequate cortisol levels.\textsuperscript{17} Determining the appropriate cortisol level in a critically ill patient is difficult.\textsuperscript{5,8,15,16,17,29} Annane\textsuperscript{21} concluded that low-dose steroid supplementation improved patient outcomes in patients dependent on exogenous catecholamines. Other studies assert that routine use of steroid supplementation cannot be justified by current data.\textsuperscript{17,8} Marik and colleagues published a consensus report in 2008 stating that the benefit of supplemental steroids may be limited to patients with vasopressor dependent shock and/or early acute respiratory distress syndrome.\textsuperscript{16} Speed of resolution of shock states was statistically improved by supplemental steroids, but no significant change in mortality rates was found.\textsuperscript{16} Marik\textsuperscript{16} concluded that adrenal function tests should not be used as a criterion for steroid supplementation. Studies that recommend glucocorticoid supplementation in the critically ill use similar dosing schedules.\textsuperscript{16,21} They suggest that patients who are not responsive to fluid resuscitation and vasopressor therapies may benefit from the use of moderate-dose (200mg/day) hydrocortisone or fludrocortisone.\textsuperscript{16,21}

\textbf{SYNTHESIS}
There are three main categories of findings into which each etomidate specific article falls regarding the safety of use; first, etomidate is safe without increase in morbidity and mortality, second, etomidate should be used cautiously due to its interference with cortisol synthesis, and third, etomidate should never be used in critically ill patients. There are two articles of Level One evidence specific to etomidate use. One suggests that etomidate should be used cautiously due to adrenal dysfunction, the other advocates that ketamine is as safe as etomidate for induction and intubation of hemodynamically unstable patients. Of the Level Two articles, seven conclude that etomidate use is safe, five conclude that it is not, and three advocate its cautious use. No article of any level refutes the decrease in cortisol production after etomidate administration, however there is no consensus in the literature as to whether etomidate is conclusively associated with worsened outcomes. Of note, the articles that advocate for the use of etomidate in the critically ill provide statistics based on the endpoints of morbidity and mortality. In contrast, the articles that advise against the use of etomidate cite data on adrenal insufficiency and the theoretical increase in morbidity and mortality without providing data that positively correlates etomidate and worsened outcomes. These three main findings should be included in the decision making process regarding the safety of etomidate for clinical use.
PART 3: INTERVENTION

INTERVENTION

The developing intervention includes creation and presentation of a Powerpoint lecture and parallel continuing education article to educate practitioners about the use appropriate of etomidate and supplemental steroids in adrenal dysfunction. The article will be submitted for publication as a continuing education course. The primary objective of the intervention is to provide education about the adrenal effects of etomidate, with a secondary objective of increased knowledge about exogenous steroid replacement treatments. The intervention will also explore alternatives to etomidate in the critically ill that will not result in adrenal suppression.
PART 4: IMPLEMENTATION

ROSSWURM-LARRABEE MODEL

The Rosswurm-Larrabee Model provides a framework by which to implement an evidence-based practice change. There are six main steps in the Rosswurm-Larrabee Model (Figure 2).

The first step is to assess for a need to change practice. The second step is to link the problem/need for change to the intended intervention and outcomes. Third, research is collected and synthesized to determine best practice. The fourth step involves the design of the practice change intervention. The fifth step requires the implementation and evaluation of the practice change intervention. The sixth and final step integrates and maintains the change after the initial intervention is complete.

Figure 3. Rosswurm-Larrabee Model
IMPLEMENTATION OF ETOMIDATE EDUCATION USING ROSSWURM-LARRABEE MODEL

Assess Need for Change

The first step in the Rosswurm-Larrabee Model requires an assessment to determine a need for the intended change. Literature review reveals a lack of consistency in knowledge and practice regarding the use of etomidate and adrenal insufficiency.

Link Problem With Interventions and Outcomes

The second step links the problem with the intended interventions and its potential outcomes. It is crucial to determine what language will be used to define the problem, interventions, and outcomes. In the case of etomidate use in the critically ill, a standard definition for several terms will need to be identified in order to remain consistent when tracking interventions and outcomes. For example, hemodynamic instability and critically ill will need to be clarified and defined with discrete terms and measurable figures. Additionally, interchangeable terminology such as adrenal dysfunction, adrenal insufficiency, and adrenocortical dysfunction/insufficiency will need to be identified. Selecting one of the terms for such instances will decrease ambiguity to improve communication regarding interventions, objectives, and outcomes. (See Appendix 1)

Synthesize Best Evidence

The third step is to refine selected interventions and outcomes using a synthesis of the literature regarding best practice. A research synthesis was performed regarding the use of etomidate in the critically ill with regard to adrenocortical insufficiency. The research synthesis included multiple studies with evidence of etomidate’s suppression of adrenal function. These studies were
evaluated to determine strength or weakness of evidence, and to identify gaps or inconsistencies in current knowledge. Quantitative evidence from randomly controlled trials and cohort studies consistently demonstrate depression of adrenal function after use of etomidate for induction of anesthesia and intubation. The synthesis concluded that there is adequate research evidence of adrenal insufficiency secondary to etomidate. Further, no evidence to the contrary was found. One of the primary conflicts regarding the conclusions of these research studies was whether etomidate should be used with caution or abandoned entirely. This conflict is significant, such that it would be untoward to conclude that etomidate should be completely abandoned. The intervention is designed to aid practitioners in determining whether the risk of etomidate is necessary and warranted on a case-by-case basis.

**Design a Change in Practice**

The next step is to design a method to influence change in practice. In this case, the lecture and continuing education module will guide the change in practice. Composition of the etomidate continuing education presentation and will be steered by the previously synthesized research and included in the CE module. A draft will be created that can be used on a trial basis to allow for feedback from practitioners.

**Implement and Evaluate Practice Change**

Several factors will be considered when finalizing the design of the etomidate presentation and continuing education module. First, content and language will be evaluated for accuracy, clarity, and concision. The content will be reviewed to determine if the covered information is
contextually useful and whether there are extraneous or conspicuously absent factors. Once the
draft has been finalized, it will be submitted for publication.

**Integrate and Maintain Practice Change**

The final step of the Rosswurm-Larrabee model is to ensure that the education results in
knowledge transfer to anesthesia practitioners who can use the information to guide their
practice.
PART 5: EVALUATION

Evaluation

Research reliably demonstrates adrenal suppression resulting from a single dose of etomidate. However, there is not clear evidence that the etomidate associated adrenal insufficiency increases morbidity and mortality. Currently, no consensus exists on how to approach induction of hemodynamically unstable patients with current pharmacological options. This lack of consistency of data or consensus prohibits creation and use of a protocol or formulaic approach to the use of etomidate.

Results

An audiovisual presentation and question and answer session was conducted on March 11, 2011 at Tampa General Hospital in Tampa, FL. Anesthesiologist, nurse anesthetists, and student nurse anesthetists were present. The CEU remains in development for publication. Further evaluation will include the performance results of the CEU to assess learning.

Outcomes

The desired outcomes of the educational interventions – audiovisual presentation and continuing education publication – will be increased provider awareness of the adrenal suppression risks associated with etomidate, the appropriate clinical use of etomidate, along with the diagnosis and treatment of adrenal insufficiency.
LESSONS LEARNED

Without confirmation of an etomidate-associated increase in morbidity and mortality, recommendations against the use of etomidate are unfounded. The evidence does not support definitive guidelines or protocols for induction agent chosen for induction of critically ill patients. Rather, the practitioner must make a clinical judgment as to whether the benefit of hemodynamic stability outweighs the risk of adrenal suppression and resulting decreased cortisol production. A decision tree that incorporates key considerations when deciding on an induction agent would be helpful to guide the decision making process and an opportunity for further DNP candidate exploration.

FUTURE DIRECTIONS

The best choice of induction agent in the hemodynamically unstable patient remains a risk versus benefit clinical judgment. This is where a decision tree may help guide, but not dictate, the clinical decision making process. Medications that are currently in development, such as MOC-etomidate, may offer additional options. As clinical research with MOC-etomidate develops, additional opportunities for DNP candidates to explore the clinical impact of this drug will become available.

Further study of morbidity and mortality associated with etomidate induced adrenal insufficiency that excludes confounding factors is warranted. There is a lack of outcomes data in the literature that definitively links etomidate with worsened outcomes.
REFERENCES


APPENDIX 1 - TERMINOLOGY

- **adrenal dysfunction**: abnormal or impaired function of the adrenal glands, in this document specifically referring to the decreased production of cortisol
  
  *Synonyms: adrenocortical dysfunction, adrenal suppression*

- **adrenal insufficiency**: inadequate production of adrenal hormones including cortisol
  
  *Synonym: adrenocortical insufficiency*

- **critically ill**: illness or trauma which requires support of ventilation, perfusion, and/or other systems to sustain life

- **hemodynamic instability**: parameters of heart rate, blood pressure, cardiac output are fluctuating outside the established normal range or requiring vasoactive medications to sustain within range
APPENDIX 2 – LITERATURE EVIDENCE TABLES

These tables were used to help sort and identify data from the articles collected during the research phase. It is not comprehensive, as more literature was identified after the initial research.

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**Level One Evidence**

**Etomidate Specific:**

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<td></td>
<td></td>
<td>Decreased responsiveness to ACTH more indicative of morbidity/mortality than cortisol itself.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discusses possible role of tissue resistance to glucocorticoids.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asserts that there is not evidence to support testing for or treatment of AI routinely in septic patients.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marik</th>
<th>2008</th>
<th>Synthesis</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consensus statement re: Corticosteroid replacement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provides specific regimen and criteria for implementation of steroid supplementation in the critically ill adults.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mesotten</th>
<th>2008</th>
<th>Synthesis CEU</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEU article.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discusses use of glucocorticoids in critical care whether or not etomidate has been given. Advocates clinical judgement rather than routine use of steroids replacement.</td>
<td></td>
</tr>
</tbody>
</table>

- Study advocates safety of etomidate
- Study advises caution with etomidate
- Study advises against use of etomidate
- Study does not make recommendations regarding etomidate
## Level Two Evidence

### Etomidate Specific:

<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Year</th>
<th>Study Type</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absalom</td>
<td>Etomidate vs thiopentone for induction in critically ill.</td>
<td>1999</td>
<td>RCT</td>
<td>No difference in morbidity/mortality or total cortisol at 24 hours, but smaller response to exogenous ACTH in the etomidate patients</td>
</tr>
<tr>
<td>Annane</td>
<td>Stop use of etomidate in the ICU for sedation, even in single dose.</td>
<td>2005</td>
<td>Editorial</td>
<td>Suggests Precedex instead.</td>
</tr>
<tr>
<td>Cotten</td>
<td>MOC-Etomidate and the differences in the effects between the analog</td>
<td>2009</td>
<td>PreClinical RCT</td>
<td>Etomidate and the differences in the effects between the analog and etomidate itself.</td>
</tr>
<tr>
<td>Cotton</td>
<td>Etomidate is a modifiable risk factor in AI in trauma patients, and should be avoided when possible.</td>
<td>2008</td>
<td>Retrospective Cohort</td>
<td>Etomidate is a modifiable risk factor in AI in trauma patients, and should be avoided when possible.</td>
</tr>
<tr>
<td>Cuthbertson</td>
<td>CORTICUS based research. Concludes that Etomidate worsens outcomes, and should be avoided in sepsis.</td>
<td>2009</td>
<td>A-priori</td>
<td>CORTICUS based research. Concludes that Etomidate worsens outcomes, and should be avoided in sepsis.</td>
</tr>
<tr>
<td>deJong</td>
<td>Cortisol response to adrenocorticotropics is inversely proportional to disease severity, and independent of blood cortisol binding. Etomidate did not contribute to mortality on a multivariate analysis.</td>
<td>2007</td>
<td>Retrospective</td>
<td>Cortisol response to adrenocorticotropics is inversely proportional to disease severity, and independent of blood cortisol binding. Etomidate did not contribute to mortality on a multivariate analysis.</td>
</tr>
<tr>
<td>Drake</td>
<td>Use of Etomidate to treat hypercortisolemia in Cushing’s.</td>
<td>1998</td>
<td>Case Report</td>
<td>Physiology of adrenal cortex, CYP450, 11β reviewed in detail.</td>
</tr>
<tr>
<td>Easby</td>
<td>Compares prehospital RSI outcomes from hypnotics – says Etomidate is best with Sux in trauma due to hemodynamics and stable ICP.</td>
<td>2004</td>
<td>Research Review</td>
<td>Compares prehospital RSI outcomes from hypnotics – says Etomidate is best with Sux in trauma due to hemodynamics and stable ICP.</td>
</tr>
<tr>
<td>Fellows</td>
<td>Sedation doses of etomidate in trauma patients in the ICU associated with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Study Type</td>
<td>Authors</td>
<td>Summary</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>Prospective</td>
<td>Gwinnutt</td>
<td>Increased mortality.</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Prospective RCT</td>
<td>Hildreth</td>
<td>Etomidate increased AI and MAY have increased mortality and length of stay.</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>RCT</td>
<td>Jabre</td>
<td>Advocates Ketamine over etomidate in critically ill and septic populations.</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>RCT</td>
<td>Mohammad</td>
<td>Cosyntropin testing - etomidate vs alternative induction agents. Found a positive correlation between etomidate and non-response to cosyntropin.</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Retrospective cohort</td>
<td>Ray</td>
<td>Adrenal supression is a minor concern in the broad picture, and correctable with steroids.</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Prospective, random control</td>
<td>Schenarts</td>
<td>Adrenal insufficiency is minor and lasts 12 hrs after RSI with etomidate, but no change in M/M.</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Prospective Cohort</td>
<td>Tekwani</td>
<td>No significant increase in length of stay or mortality when etomidate used for RSI.</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Prospective Cohort</td>
<td>Vinclair</td>
<td>Determines the duration of adrenal suppression after etomidate to be 48 hours.</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Wagner</td>
<td>1984</td>
<td>Randomized Control II</td>
<td>Etomidate causes adrenal insufficiency when used for sedation intraoperatively in otherwise healthy patients.</td>
<td></td>
</tr>
<tr>
<td>Warner</td>
<td>2009</td>
<td>Prospective cohort II</td>
<td>Increased incidence of acute respiratory distress syndrome (ARDS) and multi-organ-dysfunction syndrome with single dose etomidate.</td>
<td></td>
</tr>
</tbody>
</table>

**Glucocorticoid Specific:**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Type</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane</td>
<td>2002</td>
<td>RCT II</td>
<td>Low dose hydrocortisone &amp; fludrocortisone x 7 days improved 28 day survival in septic patients. Recommend all catecholamine dependent patients get this regimen. Not etomidate specific, but relative adrenal insufficiency specific.</td>
</tr>
<tr>
<td>Annane</td>
<td>2006</td>
<td>Inception Cohort II</td>
<td>AI is underappreciated in septic patients. Routine testing of adrenal function in sepsis is recommended. New diagnostic criteria for AI in sepsis are asserted.</td>
</tr>
<tr>
<td>Hamrahain</td>
<td>2004</td>
<td>Cohort II</td>
<td>Measurement of cortisol alone is not sufficient to diagnose abnormal adrenal function. Glucocorticoid secretion &amp; hypoproteinemia need to be measured as well.</td>
</tr>
</tbody>
</table>

**Other Resources:**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Type</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lundy</td>
<td>2006</td>
<td>Case report III</td>
<td>AI after single dose etomidate in anesthesia. Mechanism of AI after etomidate – 11β hydroxylase inhibition</td>
</tr>
<tr>
<td>Lamberts</td>
<td>1997</td>
<td></td>
<td>Good overview of AI pathology and surgical stress response.</td>
</tr>
<tr>
<td>Russwurm</td>
<td>1999</td>
<td></td>
<td>Evidence based practice model.</td>
</tr>
<tr>
<td>Egan</td>
<td>2009</td>
<td></td>
<td>Development of MOC-Etomidate and Sugammadex indicate a new age in anesthesia due to rapid metabolism or reversal.</td>
</tr>
</tbody>
</table>
DEPARTMENTAL PROTOCOL REVIEW (Student Version)

The TCU Institutional Review Board (IRB) is responsible for protecting the welfare and rights of the individuals who are subjects of any research conducted by faculty, staff, or students at TCU. Approval by the IRB must be obtained prior to initiation of a project, whether conducted on-campus or off-campus. Student research is encouraged at both the undergraduate and graduate level. Only Protocol Reviews submitted by TCU students as the Principal Investigator will be accepted for review by the Departmental IRB committee. Protocol Reviews submitted by faculty as Principal Investigators or projects that are considered above “minimal risk” need to be submitted to the TCU IRB Committee not the Departmental IRB Committee.

Please submit this protocol electronically to the Chair of your Department IRB committee. Also submit a consent document, HIPAA form if applicable, Protection of Human Subjects Training certificates, and any questionnaires, or other documents to be utilized in data collection. A template for the consent document and HIPAA form and instructions on how to complete the consent are available on the HCNHS website at the Student Research link (place the link here).

1. **Date:** September 1, 2010
2. **Study Title:** Etomidate & Adrenal Insufficiency
3. **Principal Investigator:** Amanda G Barkley
4. **Department:** Nurse Anesthesia
5. **Other Investigators:** Mark Welliver
6. **Project Period:** September 2010 – September 2011
7. **Funding Agency:** NA
8. **Amount Requested From Funding Agency:** NA
9. **Due Date for Funding:** NA
10. **Purpose:** Etomidate is a hypnotic medication known to cause adrenal dysfunction. This research will synthesize what is known about the mechanisms, treatments, and prevention of adrenal dysfunction associated with Etomidate.
11. **Background:** Etomidate
12. **Participant:** Not Applicable. No patient contact or information used. Request IRB exempt
13. **Recruitment Procedure:** Not Applicable. No patient contact or information used. Request IRB exempt
14. **Consenting Procedure:** Not Applicable. No patient contact or information used. Request IRB exempt
15. **Study:** Not Applicable. No patient contact or information used. Request IRB exempt
16. **Data Analyses** - Not Applicable. No patient contact or information used. Request IRB exempt
17. **Potential Risks and Precautions to Reduce Risk:** Not Applicable. No patient contact or information used. Request IRB exempt
18. **Procedures to Maintain:** Not Applicable. No patient contact or information used. Request IRB exempt

19. **Potential Benefits:** Educating practitioners regarding the appropriate use of Etomidate, and decreasing the morbidity and mortality associated with its use in the critically ill.

20. **Training for Protecting Human Research Participants** – Submit training certificates for all the study investigators. The training link is available on the TCU IRB webpage at: [www.research.tcu.edu](http://www.research.tcu.edu).

21. **Checklist for the Items that Need to be Submitted:** Please combine all the files into one pdf document before submitting the materials electronically to the Departmental Committee Chair. To prevent any delay in the approval of your protocol, use the most recent template for the protocol, consent document, and HIPAA form by downloading them from [www.research.tcu.edu](http://www.research.tcu.edu) or [http://www.harriscollege.tcu.edu/research.htm](http://www.harriscollege.tcu.edu/research.htm) each time you prepare your materials.

   a. Protocol
   b. Consent document
   c. HIPAA form (if applicable)
   d. Protecting Human Research Participants Training Certificate for each investigator
   e. Recruitment fliers, letters, ads, etc.
   f. Questionnaires or other documents utilized in screening and data collection
APPENDIX 4 – IRB CERTIFICATION

Certificate of Completion
The National Institutes of Health (NIH) Office of Extramural Research certifies that Amanda Barkley successfully completed the NIH Web-based training course “Protecting Human Research Participants”.
Date of completion: 11/16/2009
Certification Number: 336837
# Appendix 5 – Joanna Briggs Institute Levels of Evidence

<table>
<thead>
<tr>
<th>Levels of Evidence</th>
<th>Feasibility F(1-4)</th>
<th>Appropriateness A(1-4)</th>
<th>Meaningfulness M(1-4)</th>
<th>Effectiveness E(1-4)</th>
<th>Economic Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Metasynthesis of research with unequivocal synthesised findings</td>
<td>Metasynthesis of research with unequivocal synthesised findings</td>
<td>Metasynthesis of research with unequivocal synthesised findings</td>
<td>Meta-analysis (with homogeneity) of experimental studies (e.g., RCT with concealed randomisation) OR One or more large experimental studies with narrow confidence intervals</td>
<td>Metasynthesis (with homogeneity) of evaluations of important alternative interventions comparing all clinically relevant outcomes against appropriate cost measurement, and including a clinically sensible sensitivity analysis</td>
</tr>
<tr>
<td>2</td>
<td>Metasynthesis of research with credible synthesised findings</td>
<td>Metasynthesis of research with credible synthesised findings</td>
<td>Metasynthesis of research with credible synthesised findings</td>
<td>One or more smaller RCTs with wider confidence intervals OR Quasi-experimental studies (without randomisation)</td>
<td>Evaluations of important alternative interventions comparing all clinically relevant outcomes against appropriate cost measurement, and including a clinically sensible sensitivity analysis</td>
</tr>
</tbody>
</table>
| 3                  | a. Metasynthesis of text/opinion with credible synthesised findings  
b. One or more single research studies of high quality | a. Metasynthesis of text/opinion with credible synthesised findings  
b. One or more single research studies of high quality | a. Metasynthesis of text/opinion with credible synthesised findings  
b. One or more single research studies of high quality | a. Cohort studies (with control group)  
b. Case-controlled  
c. Observational studies (without control group) | Evaluations of important alternative interventions comparing a limited number of appropriate cost measurement, without a clinically sensible sensitivity analysis |
| 4                  | Expert opinion | Expert opinion | Expert opinion | Expert opinion, or physiology bench research, or consensus | Expert opinion, or based on economic theory |