KeT RSI: A randomized controlled trial to evaluate the hemodynamic effects of ketamine vs etomidate during rapid sequence intubation

Principal Investigator: William F. Powers, IV, MD, FACS[1]
910-667-9232
william.powers@nhrmc.org

Co-Principal Investigators: Tasha Martin, MD[1]
985-951-9201
tasha.martin@nhrmc.org

Katie Taylor, PharmD[2]
540-907-5166
katie.taylor@nhrmc.org

Co-Investigators: Lisa Hall Zimmerman, Pharm D, BCPS, BCNSP, BCCCP, FCCM[2]
Kevin Collopy, BA, FP-C, NR-P, CMTE[4]
Carrie Fales, MD[3]
Wendy Housand[4]
Steven Nakajima, PharmD, BCCCP[2]

1 Department of General Surgery New Hanover Regional Medical Center 2131 S. 17th St. PO BOX 9000 Wilmington, NC
2 Department of Pharmacy New Hanover Regional Medical Center 2131 S. 17th St. Wilmington, NC 28401
3 Eastern Carolina Emergency Physicians 4402 Shipyard Boulevard Wilmington, NC 28403
4 AirLink VitaLink New Hanover Regional Medical Center 2131 S. 17th St. Wilmington, NC 28401

INTRODUCTION/BACKGROUND:

Research thus far demonstrates that both etomidate and ketamine are safe and effective for rapid sequence intubation (RSI) in the emergent setting. Despite the reported safety of ketamine, etomidate usage continues to far surpass that of ketamine. Both etomidate and ketamine are FDA-approved for induction of anesthesia. They are both ideal drugs for intubation due to their pharmacokinetic properties including a quick onset of less than 60 seconds, a short duration of about 10 minutes, and the minimal effect they have on the cardiovascular system.

The neutral effect on the cardiovascular system is particularly important in the acute and traumatic setting when patients are often hypotensive. However, there are some differences and disadvantages in the two medications. Etomidate induces sedation by enhancing the effect of GABA, an inhibitory neurotransmitter, resulting in inhibition of excitatory stimuli. Etomidate lacks analgesic effects and has been shown to cause adrenal suppression, of which the long term significance still remains uncertain. Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) antagonist and a weak opiod agonist which results in both amnestic and analgesic properties. It is also a dissociative anesthetic and can cause profound hallucinations. There are also historical reports of ketamine causing an elevation of ICP, although newer research has not shown that effect. Due to all of these factors and limited data to support ketamine as an equal or superior alternative to etomidate, it has been difficult to clearly recommend one agent over the other for RSI.

Previous literature has evaluated the hemodynamic effects of etomidate and ketamine during RSI but these studies have been retrospective in nature.

A 2013 retrospective study by Price et al. did not find a significant difference between ketamine and etomidate in hemodynamics at any of the five post-intubation vital sign assessments. We recently conducted a retrospective comparative study on the hemodynamic effects of the two medications in the pre-hospital setting at New Hanover Regional Medical Center. There were more patients in the etomidate group to experience a decrease in SBP from pre-RSI to 15 minutes post-RSI, although the difference was not significant. We also discovered a lower SBP trend post-RSI with etomidate among the trauma and elderly population. This study was limited by the number of patients that received ketamine and was therefore underpowered.

A 2017, retrospective study was published with 968 adult trauma patients undergoing RSI in the ED with either etomidate or ketamine and results did not reveal a difference in patient-centered outcomes between the two drugs including hospital mortality, ICU-free days, ventilator-free days, vasopressor-free days, and transfusion requirements.

A prospective, randomized trial is needed to determine the superiority of one induction agent over another during this life saving measure.

AIM(S) OF STUDY:
The aim of this study is to investigate the hemodynamic effects of ketamine and etomidate in the setting of rapid sequence intubation.

OBJECTIVES:
The objective of this study is to determine if ketamine or etomidate has a better hemodynamic profile in patients undergoing rapid sequence intubation.

HYPOTHESIS:
Primary Hypothesis:
Compared to etomidate, ketamine will show an improved hemodynamic profile in patients undergoing rapid sequence intubation.

STUDY DESIGN:
This study will be a prospective randomized controlled trial evaluating the hemodynamic response in adult patients (greater than or equal to 18 years of age) undergoing rapid sequence intubation (RSI).

STUDY SETTING:
This study will be a single-center study to include pre-hospital RSI performed by New Hanover Regional Medical Centers (NHRMC) emergency transport service providers as well as emergency medical physicians performing RSI at the NHRMC emergency department located on the main hospital campus.

STUDY POPULATION:
Adult patients age 18 and greater who are not pregnant and require rapid sequence intubation will be part of the study population. Patients may require rapid sequence intubation to secure his or her airway for a myriad of reasons to include trauma, impending respiratory failure, septic shock. These patients often have labile hemodynamics in the time period surrounding intubation and the drugs used may influence this hemodynamic response.

This study is projected to treat approximately 400 subjects. Our goal is to have 200 patients in the ED settings, with 100 having etomidate and 100 having ketamine. In the pre hospital setting there will be 100 having etomidate and 100 having ketamine.

ELIGIBILITY CRITERIA:
Inclusion Criteria:
Adult patients age 18 and greater who require RSI for any indication.

Exclusion Criteria:
1. Children under the age of 18 as these patients have a different hemodynamic profile than adults and would require a separate study to clearly elucidate the effect of ketamine or etomidate during RSI.

2. Pregnant women of any age as these patients also have a different hemodynamic profile than adult patients and would require a separate study to clearly elucidate the effect of ketamine or etomidate during RSI.
3. Patients with a known hypersensitivity to ketamine or etomidate will not be administered that respective agent and will not be crossed over into the opposite group.

STUDY OUTCOMES:

Primary Outcomes:

The primary outcome will be the incidence of post RSI hypotension between patients undergoing RSI with ketamine versus patients undergoing RSI with etomidate. Post RSI hypotension will be defined as a 20% decrease in the systolic blood pressure from a patient's baseline.

Secondary Outcome(s):

Secondary outcomes will include: incidence of first pass intubation success, incidence of supplemental blood pressure agents (e.g. vasopressors) required post-RSI, time to additional sedative use

STUDY PROCEDURES:

Recruitment of participants:

Patients who require rapid sequence intubation are critically ill and are not capable of making medical decisions at the time of the procedure. During these critical moments, surrogate decision makers are rarely, if ever present and this procedure is performed as a life-saving measure to allow for further medical therapies. Informed consent of the patient nor a surrogate decision maker is possible at the time of the procedure.

Randomization:

Randomization will be assigned by calendar day beginning at midnight, with etomidate being administered to all RSI patients on even calendar days and ketamine being administered to all RSI patient on odd calendar days.

Study Procedure:

Etomidate will be dosed at a standard 0.3 mg/kg and ketamine will be dosed at a standard 2 mg/kg for the purposes of this study. Data will be collected from the pre-hospital electronic medical record for patients undergoing RSI in the pre-hospital setting and from the inpatient electronic medical record for patients undergoing RSI in the emergency department. Data extracted from each record will include ketamine or etomidate dosages and time of delivery, sets of vital signs prior to and post-intubation, number of intubation attempts, number of lost airways, dose and timing of any additional medications, requirement for additional fluid or blood product administration, indication for advanced airway placement, admitting service, lab data, past medical history, and standard patient demographics. The hemodynamic response will be measured by assessing hemodynamics for two measurements prior to administration of ketamine or etomidate and for two measurements up to fifteen minutes post administration or

until an additional sedative medication is administered. (Please separate sheet that will be placed in RedCap once IRB approval has been obtained).

Ketamine and etomidate are immediately availavle for RSI in the pre-hospital and hospital settings and are both currenly standard of care for RSI at our facility.

Data Storage:
All data will be kept in the secure database RedCap. Only study staff will have access to the database.

Safety considerations/Patient safety:
Etomidate and ketamine are both frequently used in the pre-hospital and emergency department setting with an acceptable safety profile. Etomidate has described adverse reactions to include adrenal suppression, pain at the injection site, nausea and vomiting, and nystagmus. Ketamine has described adverse reactions to include confusion/delirium, hallucinations, vivid imagery, bradycardia, increased blood pressure, nausea and vomiting, pain at the injection site, laryngospasm and nystagmus. These adverse reactions have not precluded use in routine clinical care. If a patient has a known hypersensitivity or allergy to either medication, they will not be given that medication.

STATISTICAL CONSIDERATIONS AND DATA ANALYSIS:
Sample size and statistical power: To maintain 80% power with a probability of 0.05, 200 patients will be needed in each arm to detect at 25% difference in SBP (baseline to post drug administration effects)

Statistical methods:
Data will be analyzed using SPSS with a p-value of less than 0.05 being considered significant. We will consider a 20% decrease in systolic BP from a patients baseline as significant, and will compare the incidence of post RSI hypotension between the two groups. Several a prior subgroups will be evaluated to include patients greater than 70 years of age, trauma patients requiring RSI, and those patients whose shock index is less than 0.9 versus those whose shock index is greater than 0.9.

OUTCOMES AND SIGNIFICANCE:
The results from this study will help elucidate a sedative agent that is most appropriate in unstable patients across a sepctrum of clinical scenarios to include cardiac dysfunction, severe sepsis with septic shock, trauma and the elderly.

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