Title: Comparison of Etomidate Plus Propofol, Etomidate Alone on Induction of Anesthesia

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1) Protocol Title

Comparison of Etomidate Plus Propofol vs. Propofol, Etomidate Alone on Induction of Anesthesia, a Pilot Observational Study

Protocol Version Date: *5/2/2017*

2) Objectives

The purpose of this study is compare of etomidate plus propofol vs. propofol or etomidate alone during induction of anesthesia.

The specific aims or objectives are testing patient reactions during induction, and in the post anesthesia care unit (PACU).

The hypotheses to be tested: induction with etomidate combined with propofol when compared to induction with propofol or etomidate alone:

1. will provide less pain during injection,
2. less hypotension (compare to propofol), less hypertension (compare to etomidate) and better hemodynamics than propofol or etomidate during induction,
3. Similar postoperative nausea and vomiting (PONV) when compared with propofol and less PONV when compared with etomidate,
4. Similar pain score among all three groups

3) Background

Induction of anesthesia is a critical part of anesthesia practice. Sudden hypotension, hypertension, arrhythmias, and cardiovascular collapse are threatening complications following injection of induction agent in hemodynamically unstable patients. It is desirable to use a safe agent with fewer adverse effects for this purpose.

Both etomidate and propofol are the most commonly used induction agents for general anesthesia (GA) and both propofol and etomidate have their advantages and disadvantages. Propofol has been associated with injection pain, significant hemodynamic change (hypotension) during induction and less PONV. Etomidate has been associated with more stable hemodynamic and less pain during induction, but more myoclonic movements at induction and PONV. However, those findings are still controversial and the published results are still inconsistent.

In a large retrospective study, the authors found that anesthetic induction with etomidate, rather than propofol, is associated with increased 30-day mortality and cardiovascular morbidity after noncardiac surgery. The recommended bolus induction dose is 1.5–2.5 mg/kg for propofol and 0.15–0.4 mg/kg for etomidate. One study showed that etomidate plus propofol had few effects on respiration and circulation in providing sedations for patients undergoing gastroscopy and was safer and more effective than propofol alone. In another study the authors found that with the etomidate-propofol combination (Etofol), a

milder hemodynamic response was determined compared to propofol and etomidate used alone, both at anesthesia induction and after the intubation. Etofol can be a valuable alternative in patients where cardiovascular fluctuations are not wanted. Since there are very limited published results available, it is important to provide more evidence and address the question of whether etomidate plus propofol is better than propofol or etomidate alone on induction of anesthesia.

References:

1. British Journal of Anaesthesia 110 (3): 388–96 (2013)

2. Zhou X. et al. Etomidate plus propofol versus propofol alone for sedation during gastroscopy: a randomized prospective clinical trial. Surg Endosc. March 22, 2016. DOI 10.1007/s00464-016-4861-6

3. J Cardiovasc Thorac Res, 2015, 7(4), 134-140

4. Anesth Analg. 2013 Dec;117(6):1329-37)

4) Inclusion and Exclusion Criteria

Patients will be screening for eligibility through local electronic medical record (EMR) review using the IRB-approved HIPAA Waiver for Authorization for participant identification and recruitment.

The inclusion criteria are:

- Patients scheduled for elective non-cardiac surgery
- ASA physical status of 2 or 3
- Age equal to or greater than 18 years old

Patients who do not meet the above criteria or patients who are in the following specific populations will be excluded:

- Adults unable to provide consent
- Age less than 18 years old
- Pregnant women
- Prisoners
- Difficult airway (*Mallampati class 4)*
- Morbid obesity (Body Mass Index (BMI) equal or greater than 40
- Preoperative sedation use (benzodiazepines, opioids)
- Severe cardiac (heart block, tachycardia, bradycardia, patient with pacemaker/AICD, pulmonary and liver diseases
- Hypotension and shock
- Emergency surgeries
- Allergy to propofol or etomidate

5) Study Timelines

Patients will be participating in the study for the duration of their surgery and for 24 hours after induction.

We anticipated it to take 1 year to enroll all study subjects.

We anticipate an extra 12 months after completion of the study for the investigators to complete the primary analyses.

6) Study Endpoints

The primary endpoints include:

1. Blood pressure changes during induction
2. Heart rate changes during induction

The secondary endpoints include:

1. Pain at injection
2. Myoclonic movements
3. PONV in PACU
4. Postoperative pain score
5. Incidence of adverse reactions during induction
6. Severity of adverse reactions during induction
7. Dose and frequency of vasoactive agents and other concomitant medications used to treat adverse reactions of propofol / etomidate
8. Sedation depth using bispectral index (BIS)
9. Eyelash reflex disappear time
10. Intubation time
11. Dose and frequency of analgesic and other sedatives used

7) Procedures Involved

This is a non-blinded, randomized, parallel-group study in patients scheduled for elective surgery under general anesthesia and orotracheal intubation to compare etomidate plus propofol vs. propofol or etomidate alone on induction of anesthesia.
There will be three cohorts of 25 patients per cohort with one cohort administered propofol, one cohort administered etomidate, and one cohort administered propofol

etomidate. The sample size was calculated with the blood pressure change ± 20 mmHg, SD±25 mmHg, power of 0.80 and p value of 0.05 and resulted 25 in each group.

The research team will create 75 envelopes. Each will be numbered, 25 will be in propofol group, 25 will be in etomidate group and 25 will be in propofol/etomidate group. On the day of surgery, one envelope will be randomly picked for each participant.

Patients in the three cohorts will be administered a 30 second bolus by manual hand push.

Intensive PD and safety assessments will be performed prior to dosing on Day 1 until 24 hours post-dose (Day 2). There are no plans for long-term follow-up past the 24 hours.

Three cohorts are as follow:

1. Propofol group: 2 mg/kg propofol
2. Etomidate group: 0.3 mg/kg etomidate
3. Propofol plus etomidate group: 1mg/kg propofol plus 0.15mg/kg etomidate.

Systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate will be monitored and recorded before induction, at induction and intubation followed by 1, 3, 5 and 10 minutes after intubation.

Pain on injection will be measured using 4 graded scale; 0 --- no pain, 1 --- verbal complaint of pain, 2 --- withdrawal of arm, 3 ---both verbal complaint and withdrawal of arm.

The incidence and degree of myoclonic movements also recorded as follows: 0 = no myoclonic movements, 1 = minor myoclonic movements, 2 = moderate myoclonic movements, 3 = major myoclonic movements.

The medications used in the 3 groups are clinically used already with FDA approval for their use. This is an observational study and we will compare the effects of the three groups with their medication uses on the parameters we listed above: systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, pain on injection, myoclonic movements, PONV and BIS numbers.

Non-English speaking participants are still eligible for the study. We will use translation services in line with HRP 090 and HRP 091 and the consent short form to enroll interested non-English speaking participants. If we find that we have enrolled 2 patients of a particular language using the short form as the study progressed, we will obtain full translation of the consent form into that language through the use of UCD Translation Services.

8) Data and/or Specimen Management and Confidentiality

All data will be summarized using descriptive statistics. Summaries of continuous variables will present mean, median, standard deviation, minimum, and maximum; summaries of categorical variables will present frequencies and percentages. All data will be presented in subject data listings.

Subject enrollment and disposition, including reasons for early withdrawal from the study, will summarized by group.

Demographic variables will be summarized by group for all enrolled subjects. Data will be stored up to 3 years after finishing the study.

This is a pilot study with a proposal to enroll 25 patients into each group for a total of 75 patients randomized.

We expect to complete data analysis on 20 patients in each group for a total of 60 patients due to patient withdrawal either voluntarily or due to formal withdrawal criteria, ie difficulty with securing patient airway.

9) Provisions to Monitor the Data to Ensure the Safety of Subjects

As this is a minimal risk study, there are no plans to monitor the data.

10) Withdrawal of Subjects

The PI and research team can withdraw subjects from the study without their consent if difficulty securing their airway is encountered.

11) Risks to Subjects

The potential risks are breack to confidentiality and risks associated with the study drugs, Propofol and Etomidate.

In order to safeguard our patient's confidential data and to lessen the likelihood of a breach of confidentiality, the following parameters will be put in place:

1. The data will be stored in the PI's password-protected computer in his locked office.
2. We don't anticipate needing to transport any data, but if need be, the data will be transported via a hospital issued, password protected IRONKEY.
3. Patients' names and medical record numbers will be used initially. A numerical number (0001 to 0050) will be assigned to each patient.

4. If the data need to be transmitted, the UCD secured email system will be used and the receiving end needs to be same secured email system.
5. Only the research team members can access the data.

Risks associated with Propofol and Etomidate :

Risk of Etomidate:

Transient venous pain on injection
Transient Skeletal muscle movements
Respiratory System: Hyperventilation, hypoventilation, apnea of short duration, laryngospasm, hiccup and snoring suggestive of upper airway obstruction.
Circulatory System: Hypertension, Hypotension, tachycardia, bradycardia, arrhythmias

Risks of Propofol:

Cardiovascular: Bradycardia, arrhythmia, tachycardia, hypotension, decreased cardiac output
Central nervous system: movement
Metabolic/Nutritional: Hyperlipemia
Respiratory: Apnea, respiratory acidosis during weaning
Skin and appendages: Rash, pruritus

12) Potential Benefits to Subjects

Both propofol and etomidate are used in everyday clinical practice. There are still controversial over which out of the two is better. By using the combination of etomidate and propofol at a reduced dosage in cohort 3, we hope that patients can benefit from those drugs through the minimization of side effects.

We are unable to tell if there will be a direct benefit to the study participant.

13) Multi-Site Research
N/A

14) Community-Based Participatory Research
N/A

15) Sharing of Results with Subjects
There are no plans to share study results with participants.

16) Prior Approvals
N/A

17) Provisions to Protect the Privacy Interests of Subjects

Eligible patients will be screened through electronic medical record review up to 48 hours before their scheduled elective surgery. Patients will be approached on the day of the surgery in the UC Davis preoperative holding area of the main hospital to gauge for study interest. Research team will obtain consent from interested participants and honor any withdrawal requests based off of randomization group or time-constraints.

This observational study does not allow for any interventions nor study procedures outside of the patient's normal care, so we will limit unnecessary interactions with the patients to minimize the sense of intrusiveness a subject might experience in response to standard questions, examinations, and procedures.

The research team will complete the HIPPA and required CITI training. Only at the time of data collection can the research team access the necessary patient's information.

18) Compensation for Research-Related Injury

There is no compensation for participating in this minimal risk study.

19) Economic Burden to Subjects

Both medications are already routinely ordered and administered, and will be billed accordingly to the patient's insurance.

20) Drugs or Devices
This is an observational study using FDA-approved medications that are used in everyday practice for anesthesia induction purpose.
Medication is routinely stored in PYXIS and will be taken by the anesthesiology.

21) ClinicalTrials.gov Registration

Section 1: NIH Funded Studies

If yes to BOTH, the study must be registered on Clinicaltrials.gov.

Yes	
☐	This study is funded by the NIH. (If this study is not funded by NIH, go to Section 2.)
☐	One or more human subjects will be prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Section 2: Studies subject to FDA jurisdiction

If yes to ANY the study must be registered on Clinicaltrials.gov.

Yes	
☐	This is a prospective clinical study of health outcomes in human subjects that compares an intervention with an FDA-regulated device against a control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.
☐	This is a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act.
☐	This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click here.

Section 3: Publishing the results

If yes to BOTH the study must be registered on Clinicaltrials.gov.

Yes	
☒	This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention *and* a health outcome.
☒	The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations.

This requirement includes studies of behavioral interventions.

Section 4: Registration on Clinicaltrials.gov is not required

Yes	
☐	I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research.

22) Criteria for 10 Year Approval

If yes to all items below this research may qualify for a 10-year approval period.

Yes	
☒	This research involves no more than minimal risk.
☒	This research does not receive any federal or state government funding or funding from a private funder who requires annual review per contract.
☐	This research is not subject to FDA jurisdiction.
☒	This research does not include prisoners as participants.
☒	This research is not part of an IRB reliance.
☒	This research is not subject to SCRO oversight.
☒	This research is not subject to oversight by the Research Advisory Panel of California (RAP of C).
☒	This research does not involve identifiable information held by the State of California Department or Agency
☒	This research does not involve personnel supported by federal training, center, or program grants.
☒	No personnel involved in the design, conduct, or reporting of this research have a financial interest (RFI) in this study.