HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Comparison of Methohexital with Propofol for Anesthetic induction in patients treated with an Antagonist of the Renin-Angiotensin System.

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University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

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1.0 Objectives

1.1 Study Objectives

Hypothesis: Patients on Angiotensin Converting Enzyme Inhibitors (ACEI) or Angiotensin Receptor Blockers (ARB) experience more profound hypotension upon anesthetic induction with propofol compared with methohexital.

Specific Aim 1: To determine the incidence of hypotension during anesthetic induction with propofol and methohexital in patients being chronically treated with ACEI or ARB.

Specific Aim 2: To determine the effect of propofol and methohexital on circulating neurohormones relevant to hemodynamic homeostasis in this population, namely arginine vasopressin (AVP), Angiotensin II (AII), norepinephrine (NE) and epinephrine (Epi).

1.2 Primary Study Endpoints

The primary endpoint of the study is episodes of hypotension in the 15 minutes following anesthetic induction with propofol versus methohexital. Hypotension is defined as a drop in systolic blood pressure by 30% compared to baseline systolic blood pressure and/or systolic blood pressure less than 85 mmHg. One such episode is sufficient to qualify as intraoperative hypotension.

1.3 Secondary Study Endpoints

During the first 15 minutes following anesthetic induction:
(1) The total number of doses of vasopressors (ephedrine, phenylephrine or vasopressin) administered
(2) Duration of each hypotension episode
(3) Refractory hypotension (defined as systolic blood pressure <85mm Hg following 3 doses of vasopressors)
(4) Systolic blood pressure (at 1 minute intervals)
(5) Diastolic blood pressure (at 1 minute intervals)
(6) Heart rate (at 1 minute intervals)
(7) Blood levels of AVP, AII, Epi, NE (at 3, 5, 10 and 15 min)

2.0 Background

2.1 Scientific Background and Gaps

Induction of anesthesia in patients treated preoperatively with ACEI or ARB is often associated with significant hypotension. (Rosenman et al., 2008) (Bertrand et al., 2001) One stated reason for this hypotension is the fact that antagonists of the renin-angiotensin system may reset baroreceptor function inhibiting compensatory heart rate increases in the face of hypotension. (Giudicelli et al., 1985) The intravenous induction agents, methohexital and propofol have opposing effects on this baroreceptor function; (JW, 2011) methohexital administration increases baroreceptor sensitivity with a resultant increase in heart rate, (Carter et al., 1986) while propofol decreases baroreceptor sensitivity in the face of induced hypotension. (Cullen et al., 1987; Ebert et al., 1992) Consistent with this, when induction of anesthesia in ASA Physical Class 1 and 2 patients was compared, methohexital was associated with better maintenance of heart rate and blood pressure than propofol induction.(Gold et al., 1987; Price et al., 1992) Given the significant hypotension often encountered with the use of Propofol for induction in patients on ACEI or ARB therapy(Bertrand et al., 2001; Mets, 2013; Nielson et al., 2014) and the fact that there are now increasing concerns around the use of the more cardiostable induction agent etomidate,(Komatsu et al., 2013) there is a need to establish the utility of other cardiostable induction agents for use in the increasing number of patients presenting on antagonists of the renin-angiotensin system.

2.2 Previous Data

None

2.3 Study Rationale

This study is being instituted to determine the hemodynamic stability of induction of anesthesia with methohexital or propofol in patients presenting for elective surgery who were receiving ACEI or ARB therapy. In addition, we wish to determine whether there are any different effects of these induction agents on circulating neurohormones relevant to hemodynamic homeostasis, namely arginine vasopressin (AVP), Angiotensin II (AII), and circulating norephinephrine (NE) and epinephrine (Epi).

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Adult patients (≥18 years old) treated for ≥6 weeks with ACEI or ARB
2. Patients undergoing elective surgery under general endotracheal anesthesia
3. ASA Physical Class II or III
4. Surgeries anticipated to require at least 2 peripheral intravenous catheters for adequate intravenous access

3.2 Exclusion Criteria

1. BMI >40kg/m^2
2. Taking both ACEI and ARB
3. History of difficult intubation in the past, or having anatomic predictors of a difficult airway defined as the following
    a. Mallampati Grade 3 or 4
    b. Small mouth opening
    c. Thick neck circumference (>40cm) and/or short thyromental distance
4. Require rapid sequence induction and intubation
5. Uncontrolled baseline blood pressure (SBP>180 mmHg or DBP >110 mmHg) at anesthesia preoperative clinic visit
6. Contraindication to the use of propofol or methohexital
7. Severe coronary artery disease
8. Patients scheduled for cardiac surgery
9. History of renal failure (Creatinine level >2 mg/dL)
10. Non-English speaking subjects
11. Cognitively impaired adults
12. Patient is a known or suspected difficult peripheral intravenous access

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

1. Unanticipated difficult airway
2. Unanticipated arrhythmia occurring during or immediately following anesthetic induction
3. Unanticipated adverse effect of pre-induction drugs (lidocaine, fentanyl) or induction drugs (methohexital or propofol).

4. Non-adherence to study protocol guidelines for practical reasons or safety reasons

3.3.2 Follow-up for withdrawn subjects

Not applicable

4.0 Recruitment Methods

4.1 Identification of subjects

The list of patients to present to the Anesthesia Preoperative Clinic will be reviewed on a daily basis by a provider or research associate who is directly involved in this study. All ASA Physical Class II or III patients undergoing elective surgery under general anesthesia will be identified as potential study participants. Their electronic medical record (EMR) will be reviewed by one of the study physicians in order to see whether they meet the inclusion or exclusion criteria. If they are eligible for the study, a member of the study team will approach them during their Preoperative Clinic visit, to ask them whether they would be willing to participate in this study.

4.2 Recruitment process

Patients will be recruited during their Anesthesia Preoperative Clinic visit. Either before or after they see a provider for their scheduled visit, they will be approached by a member of the research team who will briefly present them with the goals of the study as well as the risks/benefits, and gauge interest in participation. If the patient is interested in participating in the study, the attending anesthesiologist who will be administering general anesthesia for the planned surgery will personally obtain informed consent for participation in the research study on the day of surgery prior to surgery.

4.3 Recruitment materials

No recruitment materials will be used.

4.4 Eligibility/screening of subjects

Not applicable

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Consent will be personally obtained by the attending anesthesiologist in the same day unit prior to their surgery.

5.1.1.2 Coercion or Undue Influence during Consent

It will be explained to the patient that research participation is voluntary. The patient will be encouraged to ask questions and it will be explained to the patient that their decision to participate or refuse to participate in the study will have no effect on their level of care.

5.1.2 Waiver or alteration of the informed consent requirement

We are requesting a waiver of consent to review patients' records to determine preliminary eligibility. We will require access to patient EMR a few days prior to their Anesthesia Preoperative Clinic visit in order to ensure that they meet the inclusion criteria and not any of the exclusion criteria. Due to the complexity of the inclusion and exclusion criteria, the large number of potentially eligible patients and the limited research personnel available to obtain informed consent, we do not believe that this research can be practically conducted without a way to perform a preliminary screening of patients prior to approaching them for full consent. Furthermore, we are concerned that we will not obtain accurate enough data if we rely solely on patient answers without reviewing their medical record to assess for eligibility. If we deem that the patient is not a suitable study candidate, none of their PHI will be recorded. Performing a preliminary screening will also allow us to channel our research personnel efficiently and thus allow them to spend more time with potential study participants and to answer any potential questions they may have about inclusion in the study.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Written consent will be obtained. A signed and dated copy will be retained by the patient. A signed and dated copy will also be stored in the locked office of the research team and stored in the patient's medical record.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Not applicable as we are obtaining full written consent.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Not applicable

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

Not applicable

5.3.2.2 Adults Unable To Consent

Not applicable

5.3.2.3 Assent of Adults Unable to Consent

Not applicable

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Not applicable

5.3.3.2 Assent of subjects who are not yet adults

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

At the conclusion of the data collection, after data analysis, patient identifiers will be destroyed.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

We will require access to patient EMR a few days prior to their Anesthesia Preoperative Clinic visit in order to ensure that they meet the inclusion criteria and not any of the exclusion criteria. If the patient in question is not eligible for study participation, no PHI will be recorded and the patient will not be approached on the day of their Anesthesia Preoperative Clinic visit.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

As above, PHI is needed to identify potential patients prior to their Anesthesia Preoperative Clinic visit, in order for the necessary study personnel to approach the patient on the day of their preoperative Anesthesia Clinic visit, present them with the requisite information and gauge interest in participating in the study.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

Prospective, randomized clinical trial

7.2 Study Procedures

7.2.1 Post-consent assignment of anesthesiologist

After informed consent has been obtained, the anesthesiologist who will be the Chief Supervising Anesthesiologist on the day of the patient's surgery, will be notified of the name of the study patient and the date of surgery, so that one of the 3 trained anesthesiologists participating in this research study can be assigned to the patient's case.

7.2.2 Day of surgery

Randomization: The anesthesiologist assigned to administer anesthesia to the study patient will confirm the patient's study consent and ensure that the patient is still willing to participate in the study. A randomization protocol will have been created using randomization.com to randomly assign 106 patients to either the Propofol or Methohexitol groups. After the attending anesthesiologist ascertains that the patient will participate in the study, the randomization protocol will be used by a research technologist to assign the subject to a study group. The research technologist will then inform the attending anesthesiologist of which treatment the patient should receive (propofol or methohexital).

Baseline Blood Sample Collection: Patients will not receive any premedication in the preoperative area. If they experience severe anxiety, they will be given premedication although this will exclude them from study participation. Intravenous access will be established in the preoperative area by the staff anesthesiologist using 1% lidocaine for local anesthesia if the patient requests it. This IV will be used to draw blood samples preoperatively as well as intraoperatively and to administer intravenous medications and fluids intraoperatively according to current anesthetic standards of care. An appropriately-sized blood pressure cuff will then be

applied to the ipsilateral arm. An appropriately-sized blood pressure cuff shall be defined as a cuff whose bladder length is at least 80% of the arm circumference, and whose width covers 2/3 of the distance from the elbow to the shoulder. Blood samples, for baseline analysis of AVP, AII, NE and Epi levels, will be collected from the IV as follows: A tourniquet will be applied proximal to the intravenous catheter, following which 3cc of blood will be removed first to clear the 'dead space' in the intravenous line and prevent erroneous blood sampling. This blood will be discarded. A further 10cc of blood will be collected in appropriately labeled tubes (5ml in serum red top vacutainers tubes and 5ml in vacutainers tubes containing EDTA) and kept on ice until processing by our research technician, as described below. Following collection of the blood sample, 5cc of normal saline will be used to flush the line and prevent blood from clotting the catheter. A second IV will also be established in the preoperative area under local anesthesia as described above to administer intravenous medications and fluids intraoperatively according to current anesthetic standards of care.

Operating Room Procedures: Subjects will be attached to standard ASA monitors including electrocardiogram and pulse oximetry and noninvasive blood pressure monitor. Baseline blood pressure will be determined by taking three automated successive non-invasive blood pressure measurements every 1-2 minutes, until the systolic blood pressure (SBP) measurements is consistent (difference of no more than 10% between readings) with the patient lying in supine position. The averge SBP and accompanying heart rate (HR) of these three measurements will be recorded as mean baseline values.

Propofol group

Refer to Anesthesia Protocol Sheet for Anesthesiologist for specific instructions on preparation and administration of the following drugs. A crystalloid infusion will be started at a rate of 10 ml/kg/h, and 0.015mg/kg midazolam (maximum 2mg) and 1mcg/kg fentanyl (maximum 150mcg) will be administered intravenously. Patients will undergo anesthetic induction depending on whether they were randomized to the propofol or methohexital groups. Patient randomized to the propofol group will receive lidocaine 1mg/kg and propofol up to 2.5mg/kg (*total initial dose)* of propofol. The exact volume of drug (rounded to the closest milliliter) will be drawn up in two divided doses, each half-dose placed in a separate 60mL syringe. The infusion tubing that will be connected to each of the two 60ml syringes and the infusion tubing will be primed with a separate volume of study drug (measured at 2.5ml total volume for all the tubing). This same volume of study drug will remain in the infusion tubing after the infusion is complete, and therefore does not need to be added to the calculated *total initial dose* of study drug. The rate of infusion programmed on each of two Medfusion 3500 pumps will be 900cc/h. Each 60cc syringe will be placed in one of the Medfusion 3500 pumps and will be connected to infusion tubing which will, in turn, be connected to a 2-way infusion tubing splitter terminating in a single length of tubing connected to the patient's bedside intravenous (IV) catheter. This will allow each pump to operate independently and simultaneously during anesthetic induction.

If no loss of eye lash reflex results following this dose of propofol, an additional 0.5mg/kg of propofol will be administered over 30 seconds by hand (ie. not utilizing the Medfusion pumps). Following loss of eye lash reflex, patients will be given 0.6mg/kg rocuronium and will be ventilated with a tidal volume of 6ml/kg using the ventilator, for standardization of protocol. 3 minutes following administration of rocuronium, patients will undergo oral endotracheal intubation using a glidescope with a maximum of 1 attempt by the attending anesthesiologist. Following confirmation of adequate endotracheal tube placement, 2% of sevoflurane will be initiated for anesthetic maintenance with a fresh gas flow of 2L/min. Mechanical ventilation parameters will be standardized at 6ml/kg (ideal body weight) tidal volume, respiratory rate of 12 breaths/min for an end-tidal carbon dioxide concentration of 35-40mm Hg. If the

aforementioned minute ventilation is inadequate, the respiratory rate will be adjusted accordingly.

Methohexital group

Refer to Anesthesia Protocol Sheet for Anesthesiologist for specific instructions on preparation and administration of the following drugs. A crystalloid infusion will be started at a rate of 10 ml/kg/h, and 0.015mg/kg midazolam (maximum 2mg) and 1mcg/kg fentanyl (maximum 150mcg) will be administered intravenously. Patients will undergo anesthetic induction depending on whether they were randomized to the propofol or methohexital groups. Patient randomized to the methohexital group will receive lidocaine 1mg/kg and methohexital up to 1.5mg/kg (*total initial dose)* of methohexital. The exact volume of drug (rounded to the closest milliliter) will be drawn up in two divided doses, each half-dose placed in a separate 60mL syringe. The infusion tubing that will be connected to each of the two 60ml syringes and the infusion tubing will be primed with a separate volume of study drug (measured at 2.5ml total volume for all the tubing). This same volume of study drug will remain in the infusion tubing after the infusion is complete, and therefore does not need to be added to the calculated *total initial dose* of study drug. The rate of infusion programmed on each of two Medfusion 3500 pumps will be 900cc/h. Each 60cc syringe will be placed in one of the Medfusion 3500 pumps and will be connected to infusion tubing which will, in turn, be connected to a 2-way infusion tubing splitter terminating in a single length of tubing connected to the patient's bedside intravenous (IV) catheter. This will allow each pump to operate independently and simultaneously during anesthetic induction.

If no loss of eye lash reflex results following this dose of methohexital, an additional 0.5mg/kg of methohexital will be administered over 30 seconds by hand (ie. not utilizing the Medfusion pumps). Following loss of eye lash reflex, patients will be given 0.6mg/kg rocuronium and will be ventilated with a tidal volume of 6ml/kg using the ventilator, for standardization of protocol. 3 minutes following administration of rocuronium, patients will undergo oral endotracheal intubation using a glidescope with a maximum of 1 attempt by the attending anesthesiologist. Following confirmation of adequate endotracheal tube placement, 2% of sevoflurane will be initiated for anesthetic maintenance with a fresh gas flow of 2L/min. Mechanical ventilation parameters will be standardized at 6ml/kg (ideal body weight) tidal volume, respiratory rate of 12 breaths/min for an end-tidal carbon dioxide concentration of 35-40mm Hg. If the aforementioned minute ventilation is inadequate, the respiratory rate will be adjusted accordingly.

Both groups

Following induction in both groups, the blood pressure and heart rate will be measured every one minute for the first 15minutes following the administration of either propofol or methohexital, and all hemodynamic parameters (systolic blood pressure, diastolic blood pressure, heart rate) will be recorded on the data collection sheet.

Hypotension will be defined as a systolic blood pressure of less than 85 mmHg or greater than 30% decrease in the mean systolic blood pressure (as determined above), whichever is greater. If the patient develops hypotension with a systolic blood pressure of less than 85mm Hg during the 15 minutes following induction of anesthesia, the treatment algorithm outlined below will be followed (Eyraud et al., 1999; Mets, 2013):

One dose of phenylephrine will be administered if heart rate is 60 bpm or above, whereas 5mg of ephedrine will be administered if heart rate is below 60 bpm. The blood pressure will be rechecked 1 minute following, and the process repeated once or twice if necessary. If the

patient is still hypotensive following 3 total doses of vasopressors (phenylephrine and/or ephedrine), they will be considered to be in refractory hypotension and 0.5 Units of vasopressin will be administered. The blood pressure will be rechecked 1 minute following administration of vasopressin. If systolic blood pressure is still less than 85 mmHg, an additional 0.5 Units of vasopressin will be repeated once or twice as needed. Persistent refractory hypotension despite the aforementioned vasopressors will be treated with 4 micrograms of intravenous norepinephrine. All hemodynamic parameters for 15min following anesthetic induction will be recorded by the attending anesthesiologist.

Following anesthetic induction in both study groups, blood samples will be collected (as described above) at 3, 5, 10 and 15 minutes following anesthesia induction. The blood samples will be processed by dedicated research technician as described below.
Blood samples will be kept on ice at 4°C until processing. Serum samples will be allowed to clot by being left undisturbed at room temperature for 30-60 minutes. The clot will be removed by centrifuging at 1600 x g for 10 minutes @ 4°C. The liquid component (serum) will be transferred into a clean polypropylene tube using a Pasteur pipette, aliquoted, and stored @ –70°C. The plasma samples will be centrifuged at 1,600 x g for 15 minutes at 4°C and the plasma transferred to a clean microcentrifuge tube. A protease inhibitor cocktail will be added to improve the stability of desired peptides. Plasma samples will be aliquoted based on needed assay volumes and stored in -70°C until processed for data collection.

Failure to adhere to this predetermined induction and anesthetic protocol will exclude the patient from further participation in the study.

7.2.3 Following sample collection from several patients

At a later time, after samples have been collected from several study participants, serum samples will be processed to quantify Angiotensin II and plasma samples for Arginine Vasopressin, Epinephrine, and Norepinephrine using commercially available kits. Angiotensin II concentration will be determined using RayBiotech Human AngII EIA (EIA-AngII). Other markers will be measured using ELISA kits from Abnova; Arg8-Vasopressin ELISA (KA0301), Epinephrine ELISA (KA1882), and Norepinephrine (KA1891). Samples will be processed according to manufacturer's instructions.

7.3 Duration of Participation

The individual will only be participating in the study from the immediate preoperative period (after intravenous access has been established in the preoperative area) until 15 minutes following intubation. Standard anesthetic care will be provided to the individual by the attending anesthesiologist and primary provider in the room following this time, independent of study participation. There is no long-term follow-up involved for this study.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

The study drugs to be compared are Propofol (trade name: Diprivan; produced by Fresenius Kabi,USA; concentration 10mg/mL) and Methohexital (produced by PharMEDium; concentration 10mg/mL). Given several current drug shortages, prefilled methohexital syringes may not always be available from the pharmacy, in which case methohexital may have to be mixed by hand by the attending anesthesiologist. Safety precautions have been described to ensure that the

correct concentration and dose have been prepared (see section 7.4.6.3. Both propofol and methohexital are FDA approved anesthetic agents and considered standard of care. Drug inserts are provided in CATS IRB.

7.4.2 Treatment Regimen

Propofol: anesthesia will be induced using up to 2.5mg/kg of intravenous propofol administered in the manner described above (Section 7.2.2). . If no loss of eye lash reflex results following this dose, an additional 0.5mg/kg of propofol will be administered in the manner described above (Section 7.2.2).

Methohexital: anesthesia will be induced using up to 1.5mg/kg of intravenous methohexital administered in the manner described above (Section 7.2.2). If the eye lash reflex is not lost after 1.5mg/kg of methohexital, an addition 0.5mg/kg of methohexital will be administered in the manner described above (Section 7.2.2).

7.4.3 Method for Assigning Subject to Treatment Groups

The randomization scheme for this study will use variable-size, random permuted blocks to ensure that the number of participants in each treatment arm is balanced after each set of *B* randomized participants, where *B* is the block size. We will use a block size of 10. Furthermore, the randomization will be stratified by gender (male/female) and drug type (ACEI/ARB). Randomization to the propofol or methohexital arms will use 1:1 allocation. A research coordinator will access the randomization lists (developed through the website Randomization.com) stored in the secure REDCap database to randomize the participant.

7.4.4 Subject Compliance Monitoring

Not applicable

7.4.5 Blinding of the Test Article

The test drug will not be blinded

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The study drug will be obtained from the pharmacy-stocked Pyxis machines in each operating room or from the dedicated operating room pharmacy, which is standard of care.

7.4.6.2 Storage

Not applicable

7.4.6.3 Preparation and Dispensing

Refer to Anesthesia Protocol Sheet for Anesthesiologist for specific instructions on preparation and administration of study drugs. The study drugs will be prepared by one of the study anesthesiologists, and preparation and dose to be administered will subsequently be verified by another study anesthesiologist or

a study CRNA (if they are clinically available). Documentation of training by the checking anesthesiologist or certified registered nurse anesthetist (CRNA) will be required. The study team will provide a copy of the protocol and prepare a training document that summarizes the study and the checking anesthesiologist (or CRNA) responsibilities. A delegation log will be maintained to document this training. Only trained providers may act as the checking anesthesiologist for the research.

Anesthesia induction will be performed by one of the trained co-investigator anesthesiologists as described above.

The exact dose of propofol to be used for induction will be divided into two doses of identical volume, each half-dose placed in a sterile 60ml syringe by the administering anesthesiologist. The exact dose of methohexital to be used for induction will be divided into two doses of identical volume, each half-dose placed in a sterile 60ml syringe by the administering anesthesiologist. This division of doses and placement into 60ml syringes is required to attain the infusion rate required by our study protocol by using the Medfusion 3500 pumps available at our institution. Both drugs will be administered via pre-established intravenous access by using Medfusion 3500 pumps at a pre-programmed rate of infusion during anesthetic induction.

7.4.6.4 Return or Destruction of the Test Article

Residual propofol wastage is not routinely documented. Remaining drug is discarded into operating room waste containers.

Residual methohexital wastage will be handled according to protocols determined by our drug pharmacy whenever this drug is used for anesthesia induction. This includes recording the exact amount of methohexital utilized (both on the EMR and on paper) and returning all remaining methohexital to the pharmacy at the termination of surgery.

7.4.6.5 Prior and Concomitant Therapy

Not applicable.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

The total sample size will consist of 120 participants (i.e., 60 per treatment arm). A sample size of 47 subjects per group will provide 90% statistical power to detect a difference of 0.3, between the proportion of subjects having at least one hypotension episode in the propofol group compared to the proportion in the methohexital group, using a two-sided, chi-square test having a significance level of 0.05. However, we anticipate a drop-out rate as high as 20% for this study; therefore, we will enroll a total of 120 subjects.

8.2 Sample size determination

The primary outcome of this two-arm trial is the proportion of subjects that have at least one hypotension episode within 15 minutes of administration of the randomized treatment medication. A hypotension episode is defined as having a drop in systolic blood pressure >30% from baseline and/or having systolic blood pressure <85 mmHg. Eyraud et al found 42 out of 51 subjects (0.82) had at least one hypotension episode using propofol(Eyraud et al., 1999). We expect our propofol proportion to be slightly higher due to our definition of a hypotension episode and our patient population. Further, we believe an absolute reduction of 0.30 in the proportion of subjects having at least one hypotension episode in the methohexital group compared to the propofol group is clinically important. Although the randomization will be stratified by two factors (gender and drug type), to provide a conservative sample size estimate these factors were not taken into consideration for the power analysis because the correlation of these stratification covariates with the outcome would simply increase the precision, and hence, increase the power.

8.3 Statistical methods

Primary analyses will invoke an intent-to-treat paradigm, wherein all randomized subjects are included according to their randomized treatment arm, regardless of actual treatment received, compliance, etc. Data will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, and percentiles) and frequency statistics (frequencies and percentages) for categorical variables. Univariate and bivariate distributions will be inspected in order to address any missing data, inconsistent responses, outliers, and data entry errors. The sample size estimates have taken into consideration a participant drop-out of 20%; however, every effort will be made during the studies to minimize any drop-out. All hypothesis tests will be two-sided and analyses will account for the two randomization stratification factors of gender and inhibitor type. All analyses will be performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC), R software, version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria), or Stata software, version 13 (StataCorp LP, College Station, TX).

For the primary outcome of the proportion of participants having at least one hypotension episode, log-binomial regression will be used to compare the propofol and methohexital groups, adjusting for the randomization stratification factors of gender and inhibitor type. Because this is a prospective study, the log-binomial model allows us to estimate the risk ratio rather than the odds ratio while adjusting for covariates (Wacholder, 1986).

For secondary outcome of the proportion of patients experiencing refractory hypotension, the log-binomial model as described for the primary outcome will be used to compare the treatment groups. Poisson regression will be used to compare the two treatment groups, adjusting for the randomization stratification factors, with respect to the secondary outcomes of (a) the number of vasopressor doses (i.e., ephedrine, phenylephrine and vasopressin) administered per patient and (b) the number of hypotension episodes per patient over the first 18 after treatment initiation. In the event that there is an excess of zero counts, zero-inflated Poisson (ZIP) regression will be considered(Lambert, 1992).

For secondary hemodynamic outcomes of systolic blood pressure, diastolic blood pressure and heart rate over the first 15 minutes after treatment initiation, the area under the curve (AUC) for each of these variables will be calculated using the trapezoidal rule. The AUC of each these variables will be compared between the two treatment groups using linear regression models adjusting for the randomization stratification factors. A linear regression model also will be used to assess differences between the two treatment groups with respect to the duration (in minutes) of hypotension.

Blood will be collected at baseline, 3 min, 5 min, 10 min, and 15 min after treatment initiation to assess changes from baseline in AVP, AI, Epi and NE between the two treatment groups. For these continuous secondary outcomes collected longitudinally, linear mixed-effects models will be fit to compare the two treatment arms with respect to changes in these outcomes over time(Laird and Ware, 1982). The independent variables in the model will be treatment arm, time, the interaction of treatment and time, as well as the randomization stratification factors as covariates. From the mixed-effects models, contrasts will be constructed to test the hypotheses of interest with respect to changes over time in the outcomes. Linear mixed-effects models are an extension of ordinary regression models that account for the between- and within-subject correlation inherent in data involving repeated measurements per subject and allows for the variance-covariance matrix to be explicitly defined.

Following our assessment of the initial fit of the models, we will add covariates to the models that correspond to potential confounders to assess their impact, if any, on the treatment effects. Residual diagnostics will be assessed to determine the appropriateness of the model fit and, if necessary, transformations of the response will be used to meet modeling assumptions. Differences in means and associated confidence intervals (CIs) will be used to quantify the magnitude of the effects for continuous outcomes.

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

We plan to perform an interim analysis of the data collected after every 30 patients enrolled in the study, until our sample size of 120 patients is achieved. We anticipate that patients receiving antagonists of the renin angiotensin aldosterone system will experience hypotension following the administration of propofol, although this is routine practice in anesthesiology without scientific literature to contraindicate practice. Our plan to treat hypotension with vasopressors is supported by the scientific literature(Mets, 2013), although we will modify our treatment plan accordingly if we deem that it is either causing hypertension or inadequate treatment of hypotension when it occurs.

10.2 Data that are reviewed

Both propofol and methohexital have a long record of safety in anesthesia practice. However, the investigators will monitor for new safety and adverse data of these drugs as presented by medical literature to ensure that our subjects remain safe throughout the conduct of this study. Our interim analysis, as described above, will be performed using hemodynamic data (blood pressure, heart rate) and vasopressor type and dosage, as obtained from the RedCap database.

10.3 Method of collection of safety information

Any adverse effects believed to be related to the administration of study drug (as determined by anesthesiologist co-investigators in this study) will be recorded on a case report form and submitted to the PI of the study within 24 hours of occurrence.

10.4 Frequency of data collection

Due to the established safety of the 2 study drugs compared to the number of patients being studied, case report forms will be collected and analyzed after every 30 patients enrolled in the study, until our sample size of 120 patients is achieved.

10.5 Individuals reviewing the data

The data will be reviewed by the PI and anesthesiologist co-investigators on a case-by-case basis to determine whether the adverse effect (if any) is related to administration of the study drug and whether this should influence the future conduct of the study.

10.6 Frequency of review of cumulative data

After every 30 patients enrolled in the study, until our sample size of 120 patients is achieved.

10.7 Statistical tests

Not applicable, due to the established safety of the study drugs compared to the study population size.

10.8 Suspension of research

Not applicable, due to the established safety of the study drugs.

11.0 Risks

The research requires the establishment of a second intravenous line following anesthetic induction. The use of an additional intravenous line is common anesthetic practice, although (as with any invasive procedure) there is the risk of bleeding, infection at the venipuncture site and infiltration of the intravenous catheter with the infusion of medications or fluids. In this study, the line will be used to draw blood samples, but following termination of the study protocol it will be used for the administration of standard fluids and drugs required for anesthetic care.

While there is currently no evidence to suggest that either randomization arm is harmful compared to the other, there is the risk that patients will be randomized to receive an induction drug that may potentially cause more hypotension compared to the other. We will perform interim analysis of our data and stop the study should we have reason to believe that one medication is causing significant harm compared to the other. Patients will be randomized to receive either propofol or methohexital which both have the potential to cause hypotension.

Risks of propofol:

>10% incidence: low blood pressure (3%-26%), Injection site burning, stinging, or pain (18%), stop breathing for 30-60 seconds (adults 24%)

1% to 10% incidence: abnormal heart rhythm (1% to 3%), slow or fast heart rate (1% to 3%), cardiac output (volume of blood pumped by the heart per minute) decreased (1% to 3%;)

Risks of methohexital (frequency not defined but these complications are considered very rare since methohexital is considered standard of care):

Sudden stop in blood circulation due to the failure of the heart, low blood pressure, shutdown of arteries and veins in the arms and legs, fast heart rate, agitation coming out of general anesthesia, headache, anxiety, restlessness, seizures, convulsion, injection site pain, abdominal pain, nausea or vomiting, blood clot in your leg that blocks one or more of your veins, breathing problems (stop breathing, bronchospasm, cough, labored breathing, hiccups, spasm of the vocal cords making it difficult to speak or breath, inadequate breathing).

One of three trained anesthesiologists will be administering each of these induction drugs, and has the expertise to anticipate and effectively treat each of these potential complications.

There is a possible risk of loss of confidentiality of health information.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

None

12.2 Potential Benefits to Others

The results of this study will be used determine whether methohexital is a safer drug to use in anesthetic induction of patients receiving ACEI or ARBs (by causing less hypotension and less administration of vasopressor drugs). If this is the case, it may contribute to changing standard anesthetic practice and improving patient safety.

13.0 Sharing Results with Subjects

The results of this study will not be shared with subjects.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Not applicable

15.0 Economic Burden to Subjects

15.1 Costs

Not applicable

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

Recruitment will take place at the Anesthesia Pre-Operative Clinic at the University Physicians Center of Penn State Hershey Medical Center. Administration of anesthesia and research-associated blood work will be obtained in the Penn State Hershey Medical Center operating suites. Blood samples will be stored and processed in the Biomedical Research Building in Dr. Bonavia's laboratory.

16.2 Feasibility of recruiting the required number of subjects

The number of potential subjects includes any patient seen at the Anesthesia Preoperative Clinic; this generally includes most patients undergoing elective surgical procedures. We estimate one year may be required in order to recruit and collect data from 120 patients.

16.3 PI Time devoted to conducting the research

The PI has already been assigned devoted academic time by the department in order to pursue academic projects of his choosing. No additional academic time will be petitioned for on account of this project.

16.4 Availability of medical or psychological resources

Not applicable

16.5 Process for informing Study Team

Meetings will be held periodically as needed to ensure all research team members are informed about the protocol and their duties. Team emails will also be used to keep team members updated.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of the Use of Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available on the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/forms

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☒ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload the Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available on the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/forms

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

Not applicable

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility*. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require

	medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

19.2 Recording of Adverse Events

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

Not applicable

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

Not applicable

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

Not applicable

19.7 Stopping Rules

While highly unlikely to occur, the study protocol will be terminated and the patient removed from the study if the protocol interferes in any way with providing safe anesthetic care for the patient, or if any part of the protocol cannot be completed as described above, for whatever the reason.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

The principal investigator will ensure that this study is conducted and that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements. The principal investigator will be responsible for monitoring the conduct of the study and will do so on a monthly basis.

20.1.2 Safety Monitoring

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **Research Coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

The **Monitor** will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored

If the patient consents to it, their blood samples will be stored for future research. The only data labeled on specimens will be a number. No PHI will be recorded on specimens. The PHI associated with the specimen number will be stored in the secure RedCap database alone.

21.2 Location of storage

Samples will be frozen and stored in the lab of Dr. Anthony Bonavia

21.3 Duration of storage

All data and specimens will be stored for a maximum of 7 years, after which they will be destroyed.

21.4 Access to data and/or specimens

Only personnel named in the IRB at the time of initial IRB approval will have access to the data and/or specimens.

21.5 Procedures to release data or specimens

All requests to release data and/or specimens will be submitted to the Primary Investigator who is responsible for ensuring that this study is conducted and that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

21.6 Process for returning results

All results about the use of the data and/or specimens will be returned to the Primary Investigator who will ensure that they are stored in compliance with the current research protocol or future IRB-approved research protocols.

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