Effects of Premedication with Alfentanil on Hemodynamics During and Immediately Following Electroconvulsive Therapy

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Background

Electroconvulsive therapy (ECT) is a mainstay of treatment for patients with medication refractory mood disorders. The success of the therapy rests on achieving an adequate generalized tonic/clonic seizure. Multiple ECTS are usually required to achieve the desired effect. For the safety and well-being of the patient, a short general anesthetic is utilized during the ECT.

Electroconvulsive therapy is associated with brief, often dramatic hemodynamic alterations that are dangerous to the patient. This cardiovascular response is caused by activation of the autonomic nervous system and consists of an initial parasympathetic response rapidly followed by sympathetically mediated tachycardia and hypertension. The sympathetic response results in increased myocardial oxygen demand and ECT treatment has been associated with with postprocedure increases in cardiac troponin, raising concern for clinically significant myocardial injury (Duma A, et al). The ultra-short acting synthetic opioid alfentanil has a rapid onset and duration of action that mirrors the duration of hemodynamic perturbation associated with ECT while having minimal or no effect on the duration or quality of the seizure. This drug may be effective in blunting the hemodynamic perturbations associated with ECT with minimal side effects.

Alfentanil is a FDA approved narcotic utilized to blunt the hemodynamic response to stimulating portions of a procedure at the discretion of the anesthesia provider in the conduct of general anesthesia. The effect of alfentanil on patient hemodynamics immediately following ECT has been studied only once on a small number of patients (n=21) receiving etomidate anesthesia and never on patients receiving methohexital anesthesia (van den Broek, et al). Induction with methohexital as opposed to etomidate is the preferred anesthetic agent as it reduces the seizure threshold in usual induction doses. We propose a double-blind, placebo-controlled study on patients receiving ECT with methohexital anesthesia that investigates the effects of alfentanil given post-induction of general anesthesia but pre-treatment with ECT on the post-procedure hemodynamics.

Objectives

To determine if the effects of alfentanil in the course of electroconvulsive therapy reduce the hemodynamic alterations during and after treatment. The hypothesis is that pre-administration of alfentanil improves hemodynamic stability in electroconvulsive therapy.

Methods and Measures

A prospective, randomized, double blind, placebo-controlled AB/BA crossover study is planned in patients electively scheduled to undergo electroconvulsive therapy to treat their medication refractory mood disorders. We aim to have 200 evaluable treatments involving the consent of an estimated 100 subjects. As patients normally require more than 1 electroconvulsive therapy to treat their condition, the patient's consent will allow them to participate in this research study in each of two treatments.

Patients will undergo induction of general anesthesia with methohexital 1 mg/kg and succinylcholine 1 mg/kg in a standardized anesthetic protocol that is nearly identical to the usual institutional standard of care for electroconvulsive therapy. A copy of the anesthetic protocol is posted for the providers reference at the point of care. Members of the study team will be responsible for randomization of the patients and preparation of the blinded study medication. Randomization to either placebo first then alfentanil or the converse will be carried out on the morning of the first study treatment and allocation concealed within a computerized randomization and data collection instrument (REDCap). Calculation of the study dose is done per the FDA package insert using an automated system within REDCap. Alfentanil (20 mcg/kg) diluted with normal saline to 10cc or placebo, consisting of 10 cc normal saline will be obtained from the OR pharmacy and placed in an identical 10 cc syringe labeled with the patient's name and "Study Drug". Any unused quantity of alfentanil will be wasted per hospital policy in the OR pharmacy. The study drug will be administered by the blinded anesthesia provider caring for the patient per the anesthetic protocol. Data will be collected by members of the study team who are blinded to the randomization. Data will be collected and secured in REDCap stored on the institution's secure internal servers.

Inclusion Criteria

Age > /=18 years
Males or females
Anticipating electroconvulsive therapy to treat refractory mood disorders

Exclusion Criteria

Under the age of 18
Allergy to alfentanil
Allergy to other standard anesthetic medications utilized in the course of ECT (glycopyrrolate, methohexital, and succinylcholine)
History of malignant hyperthermia
History of severe airway obstruction, bronchospasm or laryngospasm
History of recent myocardial infarction, ventricular arrhythmia (within six weeks)
Adverse reaction to ECT requiring premedication with lidocaine or atropine
Non-English speaking
Patients unable to consent for themselves
Current pregnancy
Patients who have not yet received four treatments
Anesthesiologist uncomfortable with administering the study drug to the patient

Interventions and Interactions

Informed consent will be obtained during the assessment with the psychiatrist involved in their care. The patient will be randomized into 2 groups: use of alfentanil with the first treatment or placebo with the first treatment and subsequently cross over to the other therapy for the second treatment. Study medication will be prepared by a member of the study team and the patient as well as all members performing anesthesia and data collection will be blinded to group allocation. All medications utilized in the conduct of this study are the standard anesthetic medications used on a daily basis (with the exception of the alfentanil) during the course of any patient having the ECT procedure and not enrolled in a research study.

A standardized anesthetic regimen will be utilized for each subject and includes the following:

HOLDING ROOM
Glycopyrrolate 0.1 mg IV in the holding room.
Establish monitoring with baseline heart rate, blood pressures, manually recording each every 1 minute.

PRIOR TO INDUCTION
Recording 3 minutes of blood pressures, pulse oximetry and electrocardiogram, every 1 minute monitoring

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INDUCTION
Standard induction for ECT with methohexital 1 mg/kg and succinylcholine 1 mg/kg

After establishment of an adequate mask airway, and confirmation of adequate impedance on the ECT machine, the study medication (alfentanil or placebo) IV will be administered. A timer on the anesthesia monitor will be started.

60 SECONDS AFTER STUDY DRUG ADMINISTRATION
ECT stimulus applied

During the procedure in the operating room, blood pressure and heart rate will be monitored as per standard of care (blood pressure every 1 minute and continuous electrocardiogram, pulse oximetry, and capnography while in the procedure room) until the patient is spontaneously ventilating adequately per anesthesia discretion. Hypertension will be treated if the systolic blood pressure exceeds 185 mmHg using nitroglycerin 400 mcg/mL per usual institutional practice. The full range of usual antiarrhythmic, vasopressor and antihypertensive medications including lidocaine, esmolol, phenylephrine, epinephrine, atropine and ephedrine will be available for use by the anesthesia team should they be required. Use of these medications will be tracked and recorded by the study team. After restoration of adequate spontaneous ventilation the patient will then be moved to recovery for subsequent discharge. Evaluation will be done by study personnel to assess the presence of headache or other potential adverse events prior to discharge, and patient satisfaction with the anesthetic.

Prior to discharge the subjects will be asked to rate the severity of headache (if present) as well as the satisfaction with the anesthetic received. Both will be rated on a scale of 0=no headache as all up to 10=worst headache ever, as well as 0=not satisfied with anesthetic at all up to 10=most definitely satisfied with the anesthetic received.

Outcome Measure(s)

The primary outcome will be the within-individual absolute difference in systolic blood pressure from baseline to the first blood pressure after the ECT stimulus.

Secondary outcomes include the within-individual differences of heart rate at 15 and 30 seconds post stimulus, absolute difference in diastolic blood pressure from baseline to the first blood pressure after the ECT stimulus, maximum and minimum heart rates, unit doses of nitroglycerin, esmolol, phenylephrine, ephedrine, EEG and motor seizure duration, use of lidocaine, atropine or epinephrine, total in-room time, time to return of spontaneous ventilation after induction, severity of headache in the post anesthesia care unit, and satisfaction with the anesthetic post-procedure.

Analytical Plan

Results will be analyzed initially using a paired T Test for continuous variables and a Wilcoxon signed-rank test for ordinal variables.

Human Subjects Protection/Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. In addition, to ensure the participants safety and integrity of the data, the Wake Forest Institutional Data Safety Monitoring Board (I-DSMB) will be used to monitor the trial.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB or appropriate government agency if appropriate.

References

Duma A, Pal S, Johnston J, Helwani MA, Bhat A, Gill B, Rosenkvist J, Cartmill C, Brown F, Miller JP, Scott MG, Sanchez-Conde F, Jarvis M, Farber NB, Zorumski CF, Conway C, Nagele P. High-sensitivity Cardiac Troponin Elevation after Electroconvulsive Therapy. Anesthesiology. 2017 Apr;126(4):643-652.

van den Broek WW1, Groenland TH, Kusuma A, Mulder PG, Bruijn JA. Double-blind Placebo Controlled Study of the Effects of Etomidate-Alfentanil Anesthesia in Electroconvulsive Therapy. J ECT. 2004 Jun;20(2):107-11.