Electroencephalogram Studies of Induction and Recovery from Ketamine-Induced General Anesthesia

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1. BACKGROUND AND SIGNIFICANCE

General anesthesia is a man-made, neurophysiological phenomenon that has been developed empirically to enable the safe and humane performance of surgical and non-surgical procedures. The state consists of unconsciousness, amnesia, analgesia, and immobility along with maintenance of physiological stability.[1] Although general anesthesia is a neurophysiological phenomenon, until recently, approaches to studying the mechanisms of anesthetic action have focused primarily on characterizing the actions of these agents at molecular targets in the brain and spinal cord.[2-5] This important work has identified common molecular and pharmacological principles of anesthetics and has established that there are several rather than a single mechanism of anesthetic action.[6,7] Characterization of pharmacokinetic and pharmacodynamic properties, another focus of anesthesia drug research, has provided the guidelines for anesthetic drug dosing.[8] A considerable gap lies between knowing the multiple targets to which anesthetics bind, their pharmacological properties, and stating how actions at these targets lead to any behavioral state of general anesthesia. This is a problem in systems neuroscience as it requires defining how the stimulus (the anesthetic) acts in specific neural circuits to produce one or more behavioral states (unconsciousness, amnesia, analgesia, immobility).[9]

Human Studies of Anesthesia

In recent years, aided largely by non-invasive imaging methods, significant progress has been made in understanding systems-level anesthetic effects in humans. General anesthetic drugs dramatically reduce or increase (unique to ketamine) cerebral metabolism and blood flow globally across the brain.[10-16] This is consistent with our understanding that general anesthetic drugs act at multiple sites throughout the brain.[1,9] Stimulus-induced activity in primary cortical areas decreases under anesthesia,[16-20] as does functional connectivity,[21-26] though some degree of resting state connectivity has been shown to persist.[27,28] Ascending arousal systems spanning the brainstem, thalamic and cortical networks appear to become active during emergence from anesthesia-induced unconsciousness.[29,30] Disruption of anterior-posterior cortico-cortical connectivity has been proposed as a common mechanism to explain these diverse findings.[31-36] However, there is also considerable evidence to support thalamocortical[12,20,26,30,37-39] and subcortical mechanisms as well.[9]

The neurophysiological mechanisms underlying these observed changes in brain metabolism and functional connectivity remain unclear. However, anesthetic drugs are known to produce large stereotyped oscillations that may explain these brain metabolism and functional connectivity changes.[30,38-44] To bridge the gap between observed changes in brain metabolism and fMRI-derived functional connectivity, it is essential to conduct studies that can simultaneously observe fast time-scale neurophysiological dynamics across multiple functionally-connected brain regions. To understand how neurophysiology relates to time-varying states of altered arousal requires detailed behavioral characterizations. Although it is clear that unresponsiveness is not necessarily unconsciousness,[45] behavioral responses nonetheless provide crucial information on the state of altered arousal.[46,47] Most of the aforementioned work has been performed in propofol or inhaled anesthetics, and studies of ketamine are clearly needed.

Ketamine

Ketamine is an anesthetic, an anesthetic adjunct and an analgesic that acts primarily by binding to NMDA type glutamate receptors in the brain and spinal cord.[9] Ketamine is a channel blocker and thus requires an open channel to be effective.[48] Because the channels on inhibitory interneurons are generally more active than those on pyramidal neurons, ketamine primarily affects inhibitory interneurons at low to moderate doses (Fig. 1), leading typically to increased neural activity.[49,50] This is why cerebral metabolism increases with low doses of ketamine. Hallucinations, dissociative states, euphoria and dysphoria are common with low dose ketamine because brain regions, such as the cortex, hippocampus and amygdala, continue to communicate

but with less modulation and control by inhibitory interneurons. Information is processed without proper coordination in space and time.[1,9] This state is associated with high frequency beta-gamma (>30 Hz) oscillations.[51] Analgesia results most likely from the action of ketamine on glutamate NMDA receptors at the dorsal root ganglia, the first synapse of the pain pathway in the spinal cord where glutamate is the primary neurotransmitter (Fig. 1).[48]

We analyzed 4-channel frontal EEG recorded during routine monitoring in patients receiving ketamine (2mg/kg; n = 12 patients) to induce general anesthesia for surgery. As illustrated in figure 2 (middle panel), immediately after induction, we observed an alternating pattern of slow oscillations (0.1-4 Hz) and gamma bursts (30-40 Hz), Also illustrated in figure 2 (right most panel), this oscillatory dynamic eventually transitioned to persistent gamma oscillations (30-40 Hz) after several minutes. Both the slow-gamma and gamma patterns were associated with increased theta oscillations (4-8 Hz) and decreased beta/gamma oscillations (10-20 Hz).

Unfortunately, this study and those from other research groups have not provided information on how the spatio-temporal dynamics of ketamine-induced oscillatory dynamics relate to loss of consciousness, return of consciousness or hallucinatory states. This is because ketamine has been administered in a bolus fashion in these studies. Ketamine-induced EEG dynamics may aid principled approaches to brain state monitoring and targeting during general anesthesia. They may also lend insights into anti-nociceptive or pain mechanisms. Additionally, parallels between ketamine-induced hallucinatory states and clinical diagnoses associated with hallucinatory states (i.e. schizophrenia) may lend mechanistic insights into abnormal brain functioning.

Therefore, we aim to study the association between ketamine-induced neural oscillations, altered states of arousal and the perception of painful stimuli. Our central hypothesis is that ketamine-induced neural oscillations will exhibit clear distinctions between altered arousal states. Our study cohort will be comprised of healthy volunteers. We will perform assessments for hallucinations, anxiety and pain. At the conclusion of this study, we will have expanded our knowledge of the neurophysiology associated with ketamine-induced altered arousal states. The proposed human study is an integral component of our NIH P01 grant “Integrated Systems Neuroscience Studies of General Anesthesia (5 P01 GM118269) that is structured to study ketamine-induced neurophysiological dynamics across scales using recordings obtained from rodents and non-human primates, and from computational models derived from dynamical systems modeling.

2. SPECIFIC AIMS

AIM 1: To use high-density EEG recordings to characterize the different brain states induced by ketamine
Hypothesis 1.1. Ketamine gamma-burst pattern will be associated with a zero probability of response to auditory stimuli
Hypothesis 1.2. Ketamine gamma-stable pattern consists of two distinct brain states: an anesthetic state with zero probability of response to auditory stimuli and a hallucinatory state with non-zero probability of response to auditory stimuli

AIM 2: To use high-density EEG recordings to characterize oscillatory dynamics associated with the analgesic effect of ketamine
Hypothesis 2.1. Ketamine theta power will correlate with analgesia
Hypothesis 2.2. Ketamine gamma power will not correlate with analgesia

AIM 3: To use inflammatory profiling of serum to understand the effect of ketamine on systemic inflammation
Hypothesis 3.1. Ketamine-anesthesia will be associated with decreased levels of pro-inflammatory cytokines interleukin 6 and TNF-alpha
Hypothesis 3.2. Levels of pro-inflammatory cytokines interleukin 6 and TNF-alpha will correlate with a decrease in perception of painful stimuli

3. SUBJECT SELECTION

All study subjects will be American Society of Anesthesiologists (ASA) physical status classification P1. That is, all study subjects will be fit and healthy. A complete medical history will be taken and a complete physical examination will be given to rule out active and chronic medical problems.

Primary Inclusion Criteria:
Between the ages of 18 to 45
Normal body weight and habitus, BMI ≤ 30
Non-smoker
American Society of Anesthesiologists (ASA) physical status classification P1

Primary Exclusion Criteria include but are not limited to:

Cardiovascular:	myocardial infarction, coronary artery disease, peripheral vascular disease, arrhythmia, congestive heart failure, valvular disease, hypertension
Respiratory:	bronchitis, chronic obstructive pulmonary disease, smoking, shortness of breath
Hepatic:	hepatitis, jaundice, ascites
Neurologic:	seizure, stroke, positive neurologic findings on neurologic examination, multiple sclerosis, Meniere's disease, Parkinson's disease, neuropathy, peripheral stenosis
Gastrointestinal:	esophageal reflux, hiatal hernia, ulcer
Endocrine:	diabetes, thyroid disease
Renal:	acute or chronic severe renal insufficiency
Hematologic:	blood dyscrasias, anemia, coagulopathies, on anticoagulant therapy
Musculoskeletal:	prior surgery or trauma to head neck or face, arthritis, personal or family history of malignant hyperthermia
Psychiatric:	history or treatment for an active psychiatric problem, depression
Reproductive:	pregnancy, breast-feeding
Medications:	regular use of prescription and non-prescription medications expected to affect CNS function, **St. John's Wort**
Allergies:	labetalol, ondansetron, glycopyrrolate, ketamine, midazolam

Patients will be excluded from our study if they fail to pass a drug test that screens for the following: Cocaine (COC), d-Amphetamine (AMP), d-Methamphetamine (Mamp), Tetrahydrocannabinol (THC), Methadone (MTD), Opiates (OPI), Phencyclidine (PCP), Barbiturates (BAR), Benzodiazepines (BZO), Oxycodone (OXY)

Recruitment: We will select 15 volunteer subjects (male and female) between the ages of 18-45 years.
The subjects will be recruited using:
An announcement of the study distributed through the Partners Public Affairs distribution list.
The MGH Research Study Volunteer Program (RSVP).

4. SUBJECT ENROLLMENT

Procedure for informed consent: Prior to the study, each subject will sign informed consent (detailed in Screening Visit subsection of Study Design Section below). The investigator obtaining consent will explain in detail the protocol of the study, its purpose and potential benefits to society. Subjects will be informed that if they feel uncomfortable with the study, they can choose to terminate the study at any time.

Treatment Assignment and Randomization: Not applicable

Retention: All subjects who provide verbal or written consent but later decline participation in the study will not be subject to any study-related follow-up.

Remuneration: For successful completion of this protocol, subject remuneration will be $500. The subject will also be compensated for the cost of parking for their study visit.

Location: These studies will take place on White 5 at the Carl Rosow Center for Clinical Research. White 5, which is located in the cardiac anesthesia office suite, was constructed specifically for the performance of research on human subjects receiving the depressant medications used in anesthesia. The research area is built to the same standard as a typical surgical procedure room at MGH with respect to ventilation, temperature control, plumbing and electrical facilities, as well as storage. There is piped oxygen and air, wall suction and waste anesthetic gas removal. The hospital's backup generator supports electrical outlets in this location. There is a fully equipped anesthesia machine, standard anesthetic care monitors and a fully equipped code cart. The code cart and medications are checked at intervals by personnel from the OR pharmacy, and the anesthesia equipment is safety checked and maintained by Anesthesia Bioengineering. Research subjects receiving anesthetic drugs in this unit are given an identical standard of care as patients in MGH operating rooms.

5. STUDY PROCEDURES

Screening Visit: All subjects will complete a screening visit. Informed consent will be obtained during this study visit. Study subjects will undergo screening to ensure that they meet the basic inclusion/exclusion criteria for the study and give written informed consent. Study staff members will also ensure patients are enrolled in an appropriate insurance plan. Insurance coverage will be evaluated through medical record review. Each study subject will be asked to bring a copy of his/her insurance card to the screening visit. This is to ensure coverage in the unlikely event that follow-up medical care is necessary for an adverse event. All further questions will be explained as needed. A urine hCG pregnancy test and urine drug screen will be performed. Only subjects with negative tests will be enrolled.

Subjects will be given a standard pre-anesthetic physical examination. Particular attention will be paid to the subject's airway anatomy and neurologic function. Abnormal findings on physical examination may result in exclusion from the study. Abnormal findings will be reported to the subjects, and recommendations for medical follow-up will be given as needed.

A complete blood count, blood glucose level, liver function tests (LFTs), blood urea nitrogen (BUN) and creatinine (Cr) level panel will be obtained at the initial screening visit. For inclusion into the study protocol, each subject will be required to have values within the range of normal with the following exceptions: (1) AST and ALT levels within 1.5 times the upper limit of normal; (2) Alkaline phosphatase ≤ 130; (3) WBC ≥ 3.5; (4) Platelet count ≥ 120; (5) BUN within 1.5 times the upper limit of normal; (6) red cell indices. A formal exception will be obtained from the IRB for values outside of this range that represent an expected variation (i.e. increased bilirubin in a patient with known Gilbert's syndrome). Any subject who tests positive for any "street drugs" (amphetamine, barbiturates, benzodiazepines, cocaine, opiates, or phencyclidine) will be excluded from the study. Any subject who tests positive for cannabinoids may be excluded from the study if drug-abuse is suspected. A 12-lead EKG will be performed to confirm healthy cardiac functioning.

Study Visit: During the study, a board-certified anesthesiologist will be present whose sole responsibility will be to monitor (check) your safety. The sequence of this study visit will be as follows: arrival (approximately 45 minutes), baseline (approximately 15 minutes), loss of consciousness (approximately 15 minutes), recovery of consciousness (approximately 60 minutes), and discharge (approximately 45 minutes). We anticipate the study to last approximately 3 to 5 hours.

A. Arrival: Confirmation of the study subjects' fasting status (minimum 8 hours) will be made. A urine sample will be obtained for pregnancy testing in all female study subjects. The following assessments will be performed: 1.) Clinician Administered Dissociative States Scale (CADSS)[52] to assess for hallucinations; 2.) Promis Item Bank v.1.0 – Emotional Distress-Anxiety Short Form 8A modified to ask for symptoms experienced within the past hour; 3.) Promis Item Bank v.1.0 – Meaning and purpose Short Form 8A; and, 4.) Promis Item Bank v.1.0 – Positive Affect Short Form 15A (modified to ask for symptoms experienced within the past hour). The following computer presented neurocognitive assessment tests will also be performed: Global Precedence, Operation Span and Columbia Card tasks will also be administered (https://www.neurobs.com).

Standard monitors for anesthesia care monitoring including blood pressure (cuff), electrocardiogram, capnography and pulse oximetry and a 64-channel EEG montage will be placed on the subject. Video of the study subject may be recorded during baseline, induction and recovery from hypnosis periods to assess the study subject's level of arousal. Permission to record video for data analysis purposes will be obtained from the research consent form. An intravenous line will be placed for drug administration, and we will obtain approximately 15ml of blood (baseline pre-ketamine).

During this period, a calibrated cuff pain stimuli will be delivered to the gastrocnemius area of the lower leg using a validated cuff pain device (Hokanson Rapid Cuff Inflator),[53-56] titrated to 8-9/10 pain. One advantage of using cuff algometry pain is that, unlike more superficial methods (e.g. heat pain), cuff pain responses are unaffected by sensitization or desensitization of the skin.[53] The following questionnaires will be administered to assess pain intensity and quality: 1) PROMIS Numeric Rating Scale V1.0 – Pain Intensity 1A; 2) PROMIS Scale v2.0 – Neuropathic Pain Quality 5a; and, 3) PROMIS Scale v2.0 – Nociceptive Pain Quality 5a. Participants will be oriented to the following pain scale: (1) 0-1 out of 10 as "tolerable"; (2) 2-3 out of 10 as "slight discomfort"; (3) 4-7 out of 10 as "moderate discomfort"; (4) 8-9 out of 10 as "painful"; and (5) 10 as "maximum pain".

B. Baseline: A 10 to 15-minute period of EEG recording will be obtained for EEG calibration (i.e. eye movements, eye blinks, facial muscle movement) and EEG normalization (awake-eyes closed). Recordings of physiological measurements (blood pressure, heart rate, pulse oximetry, end-tidal carbon dioxide, electrooculogram, electromyogram and galvanic skin response) will be initiated and maintained from the beginning of the study protocol until the subject is ready for discharge.

C. Loss consciousness: 2mg/kg of ketamine will be infused (Medfusion pump) over approximately 5 minutes to gradually induce and allow for rapid emergence from ketamine-anesthesia. This anesthetic dose is expected to cause approximately 10-15 minutes of loss of consciousness/responsiveness. Subjects will be asked to respond to auditory stimuli via button-press jittered at random between 4 and 8 second intervals in order to resolve the precise period at which loss and recovery of consciousness/responsiveness occurred at a fine temporal scale.

General anesthetic agents, including ketamine, can produce apnea after loss of consciousness. The standard clinical approach for airway management in surgical patients is for the anesthesiologist to assist oxygenation and ventilation after the loss of consciousness. Thus, a staff anesthesiologist will use standard airway maneuvers to maintain normal oxygenation and ventilation. These maneuvers include a jaw and chin thrust and assisted ventilation with a mask and bag as part of a circle circuit. Ventilation will be manually assisted as needed. At all times, the inspired oxygen concentration, expired carbon dioxide waveform and partial pressure will be monitored continuously. The minimum inspired oxygen concentration will be 30%. The end-tidal (capnogram) carbon dioxide levels will be maintained within 10% of the baseline values. Manually assisted oxygenation and ventilation will continue until the subject recovers spontaneous ventilation. Vlisides et al. recently studied correlates of ketamine-anesthesia.[57] Because the authors rapidly administered 1.5mg/kg bolus of ketamine, the temporal correlation of EEG dynamics with loss of consciousness was not feasible in this study. Also, this study did not relate ketamine-induced altered arousal states to pain perception. While planning the present study, we spoke with the study authors and confirmed that spontaneous ventilation was maintained in all of their study subjects. They noted that nausea was frequently encountered in their study cohort. Thus, we expect that spontaneous ventilation will be maintained in our study subjects. Prior to the administration of ketamine, we will administer 4mg intravenous odansetron for the pre-emptive treatment of nausea.

Research staff will be responsible for monitoring potential side effects. An experienced board-certified anesthesiologist will always monitor and care for the subject according to the standards for delivery of anesthesia at MGH. The White 5 research unit is equipped with an anesthesia machine and physiologic data are collected electronically. This research unit has been specifically designed and equipped according to MGH standards and Massachusetts regulations as an anesthetizing location, and it has been approved for this purpose by the Clinical Practices and Safety Committee of the MGH Department of Anesthesia, Critical Care and Pain Medicine. Because ketamine may cause an increase in the heart rate and blood pressure, an

anesthesiologist may be required to administer intravenous labetalol 5 to 20 mg IV push over approximately 2 minutes for three blood pressure readings greater than 160/100. Blood pressure readings will be obtained 3-5 minutes apart. Intravenous glycopyrrolate in 0.1mg increments may also be administered for excessive salivary secretion. In order to minimize external stimuli, ketamine administration will occur in a room with low lighting and minimal noise. Based on the acuity of physiological or behavioral changes, the anesthesiologist may modify these treatment recommendations.

The study investigator will be available over the phone at anytime to address any concerns. Subjects will be advised to contact the study PI for any medical related concerns. The study PI may advise subjects to obtain follow-up care from their nearest emergency department or primary care physician. Study staff will use the EPIC alert system to monitor subject admittance to any Partners Hospital. The study investigator will contact all study subjects 24 hours after completion of the study visit to address any concerns or study related adverse effects.

D. Recovery of consciousness: We will conduct assessments 5-minutes after recovery of consciousness and at approximately 15-minute intervals after recovery of consciousness for a total of three assessments. These assessments will consist of: 1.) CADSS; 2.) Promis Item Bank v.1.0 – Emotional Distress-Anxiety Short Form 8A modified to ask for symptoms experienced within the past hour; 3.) Promis Item Bank v.1.0 – Meaning and Purpose Short Form 8A; and, 4.) Promis Item Bank v.1.0 – Positive Affect Short Form 15A (modified to ask for symptoms experienced within the past hour. After these assessments, the cuff pain device will be inflated (pre-calibrated pressure; see Arrival subsection above), and pain intensity and quality assessments will consist of: 1.) PROMIS Numeric Rating Scale V1.0 – Pain Intensity 1A; 2.) PROMIS Scale v2.0 – Neuropathic Pain Quality 5a; and, 3.) PROMIS Scale v2.0 – Nociceptive Pain Quality 5a.

After the third assessment (i.e. approximately 35 minutes after recovery of consciousness), we will administer 0.05 mg/kg of midazolam (maximum dose of 4 mg) to resolve ketamine-induced perceptual disturbances. Midazolam is routinely administered during the peri-operative period to mitigate ketamine-induced perceptual disturbances. Approximately 5 minutes after midazolam is administered, we will resume assessments for a minimum of two assessments (approximately 55 minutes after recovery of consciousness) or until the subject is ready for discharge. We will obtain approximately 15ml of blood (post-ketamine, pre-midazolam). The following computer presented neurocognitive assessment tests will also be performed: Global Precedence, Operation Span and Columbia Card tasks will also be administered (post-ketamine, pre-midazolam).

E. Discharge: If medically stable, as deemed by a board-certified anesthesiologist, the intravenous line and physiological monitoring devices will be discontinued, and subjects will be discharged home with a responsible family member or other adult caretaker. Discharge home will be based on criteria established by the MGH Department of Anesthesia practices for discharge from the hospital following ambulatory surgery. The subject must have stable vital signs, be able to respond appropriately to normal commands, be pain free, be free from any nausea and vomiting and have no bleeding from the intravenous sites. Subjects must be able to walk unassisted and have an accompanying adult to escort them home. Subjects will be advised against returning to work and driving or operating heavy equipment for 24 hours.

If subjects experience adverse events at home, they will be referred for evaluation at the nearest emergency department. These instructions will also be provided to the responsible adult escort prior to discharge. The subject's individual insurance plan will be responsible for covering this visit.

6. BIOSTATISTICAL ANALYSIS

EEG acquisition Preprocessing: Continuous 64-channel EEG will be recorded. All data will be stored for subsequent off-line analysis. We will apply an anti-aliasing filter and down-sample the EEG data to reduce computational complexity before analysis. Bandpass filtering of the acquired signal will vary depending upon

the features of the EEG data of interest. Trigger signals will be sent from the stimulus delivery system to the EEG recording system to tag the stimulus events for subsequent binning, temporal epoching and averaging of EEG data into the relevant evoked potential averages.

Spectral Analysis: We will compute spectrograms for all subjects using the multitaper method. We will also compute group-level baseline-normalized spectrograms for induction and emergence by taking the median across subjects with the data aligned to the LOC and ROC time points, respectively. To assess statistical significance for the difference in EEG spectra at each frequency, we will compute the 99% confidence interval of the median difference between groups by using an empirical bootstrap approach. The null hypothesis will be rejected only if the confidence interval of the median difference at each frequency exceeds the significance threshold over a contiguous frequency range ≥ 2W.

Eigenvalue and Modal Projection Analyses: We will perform an eigenvector decomposition analysis of the cross-spectral matrix to identify the principal modes of oscillation in the conscious and unconscious states and to analyze how activity within these principal modes changes through time. We will estimate the cross-spectral matrices $P_{baseline}(f)$ and $P_{unconscious}(f)$ at each frequency *f* using the multitaper method using data from the full baseline period, as well as segments of at least 5 min extending from LOC to ROC, respectively, for each subject. An eigenvalue decomposition of the median cross-spectral matrix at each frequency will be performed. Each eigenvector describes a coherent spatial distribution or mode of oscillation, and the corresponding eigenvalue quantifies the power in this mode. We then use modal projection analysis to characterize how power within principal modes change as a function of time. A permutation-based procedure will be performed to assess statistical significance for the modal projection analysis.

Behavioral Analysis: The probability of response to verbal stimuli and the difference in probability of response will be estimated by using Bayesian Monte Carlo methods to fit a state-space model to these data. To perform group-level analyses, we will align the behavioral data across subjects with respect to each subject's LOC time for induction and with respect to each subject's ROC time for emergence. We will then pool the responses, and pooled data will be used to estimate group-level probabilities of response using the state-space model.

Inflammatory profile Analysis: Plasma samples will be submitted to Myriad/Rules Based Medicine (Myriad RBM, Austin, TX, USA) for analysis using their proprietary platform. Wilcoxon rank-sum tests with corrections for multiple comparisons will be used to assess analyte differences. In exploratory analyses, we will examine Pearson correlations between analytes and variables of interest (i.e. pain, anxiety).

Power Analysis: Assuming the point estimate for gamma power at baseline is -20 dB and 5 dB for ketamine induced-unconsciousness (**Fig 2**.), a standard deviation of 20 dB, type 1 error of 0.05, and desired power of 0.9, n =14 study volunteers will enable us to detect a gamma power ratio of 25 dB. Therefore, we aim to recruit up to 15 subjects.

7. RISKS AND DISCOMFORTS

EEG risks: The risks associated with EEG electrodes are redness and irritation at the placement site.

Questionnaire risks: Minimal risks associated with completing questionnaires are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning.

Data risks: Procedures are in place to reduce the likelihood of a breach of confidentiality including the de-identification of data and storage of data only on Partners approved devices/portals. However, there is a small risk that people outside of this study may be exposed to information about study subjects.

Ketamine: Although it has a good safety profile overall, ketamine has documented sympathomimetic activity that may result in mild to moderate increases in heart rate, blood pressure and cardiac output, though this activity is generally short-lived.[58] Other possible side effects reported during ketamine infusion include arrhythmia, increased salivation, increased bronchial secretions, horizontal nystagmus, euphoria and

hallucinations. Nystagmus may persist for a period after the ketamine infusion has terminated. Any acute changes in physiology, such as changes in heart rate or blood pressure, will be treated using standard anesthesiology practices. Rare side effects are allergic reactions (skin rash), pain at the site of injection, increased intraocular pressure, ulcerations and inflammation in the bladder (reported in ketamine abusers). Ketamine is a controlled substance and has the potential for abuse and dependence, particularly in subjects with history of drug abuse. Subjects with history of substance abuse or dependence will be excluded.

Glycopyrrolate risks: Risks involved in the administration of glycopyrrolate include hypertension and tachyycardia.

Labetalol risks: Risks involved in the administration of labetalol include hypotension and bradycardia.

Cuff pain stimuli risks: Risks of cuff pain include mild transient bruising associated with inflation of the cuff. Our previous experience has also demonstrated that pain ratings go down to nil within several seconds of stimulus termination. A button press rapidly deflates the cuff, ensuring subject safety.

Blood draw risks: Pain at the needle insertion site, infection, and bleeding.

8. POTENTIAL BENEFITS

Subjects will have no direct benefit from taking part in this study. Ketamine-induced EEG dynamics may aid principled approaches to brain state monitoring and targeting during general anesthesia. They may also lend insights into anti-nociceptive or pain mechanisms.

9. MONITORING AND QUALITY ASSURANCE

The principal investigator and co-investigators will be responsible for monitoring and quality assurance of the study. In conjunction with the research assistants, weekly meetings will be held and documented. Current subjects in the study will be discussed at each meeting, and charts will be reviewed for completeness. The team will evaluate the progress of the study; verify that the rights and well being of the subjects are protected; ensure that the reported study data are accurate, complete and verifiable from source documents; and assure the conduct of the study is in compliance with the approved protocol and amendments.

Serious Adverse Events: Expedited review will occur for all events meeting the FDA definition of SAEs – i.e., any events that are fatal, immediately life-threatening, permanently or substantially disabling, or requiring/prolonging inpatient hospitalization. This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect or precaution. Reporting to the IRB will be done within 24 hours of the SAE.

Study Stopping Rules: If at any time during the course of the study the PIs or CO-Is judge that risk to subjects outweighs the potential benefits, the PI/CO-Is shall have the discretion and responsibility to recommend that the study terminated.

AE Reporting Guidelines: Unanticipated problems involving risks to subjects or others including adverse events will be reported to the PHRC in accordance with PHRC unanticipated problems including adverse events reporting guidelines, as well as the RDRC within 5 days.

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