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Department of Anesthesiology

STUDY PROTOCOL

TITLE: **Modulation of long-term memory by the experience of pain during sedation with anesthetics**

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Description of research activities

The study will be performed in 2 phases. All subjects will undergo Phase 1, and a subset will undergo functional MRI while performing the same experimental protocol during Phase 2. Adult subjects (age 18-59) will be enrolled from the general population. Exclusion criteria are designed to prevent confounding results by factors known to affect memory performance or anesthetic drug responsiveness: age greater than or equal to 60 years, psychotropic medication use, and BMI>30. Because of the inherent use of words in the experiment, subjects will be excluded if English is not their primary language. Further exclusion criteria are to prevent harm from the anesthetics including pregnancy and any contraindications to anesthetic care. Subjects will additionally be excluded from Phase 2 if they have any MRI-incompatible implants or foreign bodies. Subjects will be instructed to abstain from solid food and any glucose or caffeine for 8 hours, and from clear liquids for 2 hours prior to visits that will involve drug administration. Subjects will be reminded that they are free to withdraw at any time. Subjects will not be permitted to drive after receiving the sedative agents and will be advised to plan for alternative transportation after the visits of the study that involve medications.

Phase 1 of the study will occur over the course of three visits, with two anesthetics to be tested in randomized, cross-over fashion. A phone call and email prior to the 1st session will screen subjects for any exclusion criteria and describe all experimental procedures and the risks. On arrival for the first session, the research protocol will be reviewed, and consent obtained after all questions answered. Subjects will then complete psychological tests for sleepiness (using the Epworth sleepiness scale), stress (using the Brief Inventory of Perceived Stress), depression (using the Beck Depression inventory 2), and anxiety (using the State-Trait Inventory for Cognitive and Somatic Anxiety, STICSA). An electric nerve simulator (EZStim II, Life Tech Inc., approved by the FDA and under PRO10020252) will be applied to the subject's left index finger and current level slowly titrated to their subjective rating of 5/10 pain, as in previous studies. Subjects will specifically assess whether the level of pain will impair their ability to participate in the experiment. This self-adjusted current level will be employed for brief painful stimulation during memory encoding. These screening and psychometric tests are expected to take 15 minutes total.

The memory encoding experiment will involve listening to a list of 90 recorded words played via headphones. One-third (30) of these words will be consistently paired with painful ENS, and the order of these randomized among words not paired. Words will be displayed for 1s and the shock (if present) will be 1 s in duration coinciding with the word appearance. The subjects will then have 2 s to perform a categorization cognitive task for each word, which has previously been shown to produce "deep" memory encoding. By pressing of one of two buttons (with different fingers), subjects will indicate, for example, if the cue word represents something living versus non-living. Response time and accuracy will be electronically recorded. When the first decision-making battery is complete, the decision task will change. For example, subjects may be instructed to now decide if the word represents something abstract or concrete. The same list of 90 words will then be repeated, in random order, with the same 30 words paired with ENS. A similar (but distinct) lexical decision task will be used for a third battery, giving three total encoding opportunities for the word list under the no-drug condition. The entire set of 3 tests is anticipated to take 15 minutes.

Based on a computer-generated random number, the subjects will be randomized into two equal groups that determine which anesthetic drug they will receive in the first visit. All subjects will then receive the other drug in the second visit; all subjects will receive both drugs in counter-balanced fashion. Whichever anesthetic has been randomized to be administered first will be titrated using a target-controlled infusion strategy for effect-site concentration; doses previously shown produce 40% amnesia (60% long-term recall). This approach should achieve and maintain, based on subject parameters and drug pharmacokinetics, a steady-state plasma concentration of the drug that is equal across subjects. Because the subject's sedative response to the medications is known to vary (in fact, this is one of the dependent variables to be measured in the study) drugs are not dosed or titrated to a specific observer-rated level of sedation. However, the level of sedation is expected to range between no perceptible sedation to light sedation, in which subjects follow verbal commands. Certainly, if any subject fails to respond to the auditory cues, the infusion will be stopped or decreased to empirically guide the dosing strategy to a level of light sedation in which they are able to respond to the auditory stimuli that are required for the experiment. The initial effect-site concentrations to be targeted will be 0.15 ng/ml for dexmedetomidine and 0.4 ng/ml for midazolam. These targeted concentrations may also be adjusted based on a preliminary analysis of the level of long-term memory observed from the first 2 subjects, with a range of 40-70% amnesia acceptable. The infusion parameters will be custom calculated, using the well-established STANPUMP software (from Steven Shafer, MD, Palo Alto VAMC) for each subject based on age, gender, weight, and height. Doses will not exceed the manufacturer's recommended doses for procedural sedation for both agents. All sedation will be performed in the MRRC, and the standards for monitoring during anesthetic administration established by the American Society of Anesthesiologists will be used; this standard has been uploaded as an attachment to the protocol.

Once drug steady state is reached, approximately 10 minutes later, subjects will undergo three batteries of decision-making tasks with a second independent list of words, using the procedures described for the no-drug condition. This second set of 3 batteries of memory encoding is expected to take 15 minutes. Immediately after the experimental procedures, subjects will be asked to again complete the STICSA, to account for changes in anxiety level as a result of the experimental procedures and/or drug administration. At the conclusion of the experiment, subjects will be allowed to fully recover from the anesthetic prior to discharge and asked not to operate a car or machinery the rest of the day. The recovery period will vary based on each individual subject's recovery profile, and this expected to take between 1 and 2 hours. The total time spent for the visit will thus be between 2 and 3 hours.

The second visit in Phase 1 will occur 1 - 3 days later. Subjects will begin with long-term memory testing for the items from visit 1, using the remember-know procedure. In brief, all words from both lists will be played in random order, with some intermixed novel distractor words (to account for guessing). Subjects will decide for each if they remember it (specifically recall), know it (feel is familiar), or think the word is totally novel. This testing is expected to take 30 minutes. Subjects will then repeat all the experimental procedures described for visit 1, using two different words lists and the drug not used in visit 1. The total time for the memory encoding experiment will again take 1 hour, with 1-2 hours for anesthetic recovery. Thus, visit 2 will be a total duration of 2.5 to 3.5 hours.

The third visit in phase 1 will be scheduled 1 - 3 days after visit 2 and consist only of long-term memory testing as described. This brief visit will only take 30 minutes. The total time spent for all 3 visits will vary between 5 to 7 hours. As each visit is separated by 1 to 3 days (to accommodate subject's scheduled), all procedures for Phase 1 of the study and will occur over 3 to 9 day period.

Phase 2 of the study will include a subset of subjects from Phase 1. Any subject that is available and willing to participate in Phase 2 will be eligible to do so as long as there were no technical issues with their behavioral data from Phase 1. That is, if the subjects had an inadequate or excessive response to one or both of the anesthetics, or if they did not properly perform any aspect of the learning task or memory tasks they will be excluded. Subjects will also be excluded from Phase 2 if they cannot tolerate the scanner due to discomfort or claustrophobia, which will be assessed by a mock scanner session prior to Phase 2 - Visit 1, during which the actual scanner will be used for data acquisition. Subjects will further be excluded from Phase 2 if the MRI environment would be unsafe for them (and this either changed or somehow failed screening during Phase 1), if they have a positive pregnancy test (this will be administered to all females with child-bearing potential prior to Phase 2). Because the imaging portion of the study would be futile without the successful formation of long term memories under the sedation, subjects will be also be excluded from Phase 2 if they have less than 10% long-term retention of presented cues from their least successful session. In addition, subjects planned to participate in Phase 2 will first

undergo a short session in which they can familiarize themselves with a MRI scanner mock-up, to ensure they can perform the experiment while lying in a tube without undue anxiety or discomfort. All experimental protocols are intentionally designed to be portable to the MRI environment. Thus, in Phase 2, the subject's brains will be imaged while performing the same auditory memory task with periodic pain stimulation under no-drug and both drug conditions, again randomized. Repeat visits with memory testing and subject cross-over to the other drug condition will occur in the same manner and on the same timeline as in Phase 1. Thus Phase 2 consists of 3 visits of lengths of 2-3 hours, 2.5-3.5 hours, and 30 minutes.

For each visit in Phase 2, subjects will complete the same psychometric testing items described for Phase 1. They will then be screened with the standard questionnaire by the MRRC staff to ensure safety within the MRI. The volunteer will then change into MR safe clothing, if necessary, and this would be in private. Next, they will meet with the anesthesiologist who will administer the sedation and monitor their vital signs during the experiment. The anesthesiologist will review the subject's medical history, perform a focused history and physical, and obtain intravenous access. The nerve stimulator will be adjusted to their subjective rating of 5/10 pain, in the same manner previously used. The subject will be positioned in the scanner, given appropriate hearing protection, and re-familiarized with the response button equipment to be used for the experiment.

Imaging will performed using a Siemens 3.0 T Trio Scanner (Siemens Medical Solutions, Malvern, PA). The imaging protocol will consist of continuous BOLD imaging during the learning experiments. All fMRI data will be acquired with a BOLD-weighted gradient echo sequence with the following parameters: TR (repetition time) 2 s, TE (echo time) 30 ms, flip angle 90, matrix 64 x 64, in-plane resolution 3.125 x 3.125 mm and slice thickness 4 mm. Thirty-five contiguous axial slices will collected in an interleaved fashion, providing whole brain coverage. For each subject, a high-resolution T1-weighted image will be acquired during titration of the study drug. This anatomical image will be acquired with a 3-D magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence with following parameters: TR 2.5 s, TE 5 ms, flip angle 35, matrix size 256 x 192, field of view 20 cm, in-plane resolution 1.2 mm, and slice thickness 2.8 mm, contiguous. Timing from the scanner will be synchronized such that the image at the time of presentation of a word cue can be retrospectively analyzed separately for successful vs unsuccessful encoding into long-term memory.

American Society of Anesthesiologists®

STANDARDS FOR BASIC ANESTHETIC MONITORING

Committee of Origin: Standards and Practice Parameters

(Approved by the ASA House of Delegates on October 21, 1986, last amended on October 20, 2010, and last affirmed on October 28, 2015)

These standards apply to all anesthesia care although, in emergency circumstances, appropriate life support measures take precedence. These standards may be exceeded at any time based on the judgment of the responsible anesthesiologist. They are intended to encourage quality patient care, but observing them cannot guarantee any specific patient outcome. They are subject to revision from time to time, as warranted by the evolution of technology and practice. They apply to all general anesthetics, regional anesthetics and monitored anesthesia care. This set of standards addresses only the issue of basic anesthetic monitoring, which is one component of anesthesia care. In certain rare or unusual circumstances, 1) some of these methods of monitoring may be clinically impractical, and 2) appropriate use of the described monitoring methods may fail to detect untoward clinical developments. Brief interruptions of continual† monitoring may be unavoidable. These standards are not intended for application to the care of the obstetrical patient in labor or in the conduct of pain management.

1. STANDARD I

Qualified anesthesia personnel shall be present in the room throughout the conduct of all general anesthetics, regional anesthetics and monitored anesthesia care.

1.1 Objective –

Because of the rapid changes in patient status during anesthesia, qualified anesthesia personnel shall be continuously present to monitor the patient and provide anesthesia care. In the event there is a direct known hazard, e.g., radiation, to the anesthesia personnel which might require intermittent remote observation of the patient, some provision for monitoring the patient must be made. In the event that an emergency requires the temporary absence of the person primarily responsible for the anesthetic, the best judgment of the anesthesiologist will be exercised in comparing the emergency with the anesthetized patient's condition and in the selection of the person left responsible for the anesthetic during the temporary absence.

2. STANDARD II

During all anesthetics, the patient's oxygenation, ventilation, circulation and temperature shall be continually evaluated.

2.1 Oxygenation –

2.1.1 Objective –

To ensure adequate oxygen concentration in the inspired gas and the blood during all anesthetics.

2.2 Methods –

2.2.1 Inspired gas: During every administration of general anesthesia using an anesthesia machine, the concentration of oxygen in the patient breathing system shall be measured by an oxygen analyzer with a low oxygen concentration limit alarm in use.*

2.2.2 Blood oxygenation: During all anesthetics, a quantitative method of assessing oxygenation such as pulse oximetry shall be employed.* When the pulse oximeter is utilized, the variable pitch pulse tone and the low threshold alarm shall be audible to the anesthesiologist or the anesthesia care team personnel.* Adequate illumination and exposure of the patient are necessary to assess color.*

3. VENTILATION

3.1 Objective –

To ensure adequate ventilation of the patient during all anesthetics.

3.2 Methods –

3.2.1 Every patient receiving general anesthesia shall have the adequacy of ventilation continually evaluated. Qualitative clinical signs such as chest excursion, observation of the reservoir breathing bag and auscultation of breath sounds are useful. Continual monitoring for the presence of expired carbon dioxide shall be performed unless invalidated by the nature of the patient, procedure or equipment. Quantitative monitoring of the volume of expired gas is strongly encouraged.*

3.2.2 When an endotracheal tube or laryngeal mask is inserted, its correct positioning must be verified by clinical assessment and by identification of carbon dioxide in the expired gas. Continual end-tidal carbon dioxide analysis, in use from the time of endotracheal tube/laryngeal mask placement, until extubation/removal or initiating transfer to a postoperative care location, shall be performed using a quantitative method such as capnography, capnometry or mass spectroscopy.* When capnography or capnometry is utilized, the end tidal CO2 alarm shall be audible to the anesthesiologist or the anesthesia care team personnel.*

3.2.3 When ventilation is controlled by a mechanical ventilator, there shall be in continuous use a device that is capable of detecting disconnection of components of the breathing system. The device must give an audible signal when its alarm threshold is exceeded.

3.2.4 During regional anesthesia (with no sedation) or local anesthesia (with no sedation), the adequacy of ventilation shall be evaluated by continual observation of qualitative clinical signs. During moderate or deep sedation the adequacy of ventilation shall be evaluated by continual observation of qualitative clinical signs and monitoring for the presence of exhaled carbon dioxide unless precluded or invalidated by the nature of the patient, procedure, or equipment.

4. CIRCULATION

4.1 Objective –

To ensure the adequacy of the patient's circulatory function during all anesthetics.

4.2 Methods –

4.2.1 Every patient receiving anesthesia shall have the electrocardiogram continuously displayed from the beginning of anesthesia until preparing to leave the anesthetizing location.*

4.2.2 Every patient receiving anesthesia shall have arterial blood pressure and heart rate determined and evaluated at least every five minutes.*

4.2.3 Every patient receiving general anesthesia shall have, in addition to the above, circulatory function continually evaluated by at least one of the following: palpation of a pulse, auscultation of heart sounds, monitoring of a tracing of intra-arterial pressure, ultrasound peripheral pulse monitoring, or pulse plethysmography or oximetry.

5. BODY TEMPERATURE

5.1 Objective –

To aid in the maintenance of appropriate body temperature during all anesthetics.

5.2 Methods –

Every patient receiving anesthesia shall have temperature monitored when clinically significant changes in body temperature are intended, anticipated or suspected.

† Note that "continual" is defined as "repeated regularly and frequently in steady rapid succession" whereas "continuous" means "prolonged without any interruption at any time."

* Under extenuating circumstances, the responsible anesthesiologist may waive the requirements marked with an asterisk (*); it is recommended that when this is done, it should be so stated (including the reasons) in a note in the patient's medical record.