ClinicalTrials.gov Document cover page

Official Title: Neural Correlates of Lidocaine Analgesia

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Study Protocol

Participants will be recruited from the community by several methods of advertising. Eligible subjects will be emailed a copy of the consent form, at least 24 hours to review the form. If subjects express continued interest in enrolling in the study, they will continue to enrollment.

A phone discussion with the PI will be scheduled, and consent will be completed in advance of the study visit, using real-time 2-way discussion over the phone and electronic capture of consent using RedCap. After consent, the subject will be scheduled for their study visit, and reminders sent by email/text at their preference.

Subjects will be given instructions for several pre-visit restrictions. 1 - They will be asked to abstain from caffeine intake for 8 hours prior to their visit. This ensures that the vasoconstrictive effects do not interfere with the blood flow response on which fMRI depends (avoiding an experimental confound). 2- The participant will avoid any solid food, fat, or protein intake for 8 hours prior to their visit. Subjects will also avoid clear liquids for 2 hours prior to the visit, for the same reason. This is to ensure their stomach is empty and to prevent a possible complication of regurgitation or aspiration, consistent with American Society of Anesthesiologists guidelines for preoperative oral intake.(1) 3 - Female subjects will be asked to not urinate in the hour before the visit, so that they are easily able to void on arrival, and a urine sample can obtained in a timely manner.

Subjects will also be instructed on the post-visit restriction to not drive a vehicle or operate machinery immediately after receiving lidocaine. They will be informed that they will need to arrange for a way to get home (without driving) from the study visit.

On arrival, subjects will be met by a member of the study team in the BST3 lobby, and be escorted through the secure facility to the 7T research scanner in the basement. Urine sample will be obtained from female subjects (private bathroom is available), and pregnancy test will be performed on the sample. Subjects will be informed of the result.

A nerve stimulator (EZ Stim II, LifeTech; currently being used in STUDY19030183) will be connected to a finger with two small electrodes. A low amplitude electrical current will then be delivered. Starting at zero, the intensity will slowly be increased until they report a pain of 7 out of 10, where 0 is no pain and 10 is intolerable pain. The nerve stimulator will then be turned off and then used periodically for 10 seconds at a time during the subsequent portions of the experiment. Unless the subject requests an adjustment, the level of current delivered will not be changed after initial adjustment.

A physician anesthesiologist will interview the subjects and do a brief physical exam to ensure it is safe to receive lidocaine. This will include questions about medical conditions, past surgeries, medications, allergies, and any active symptoms. The examination will consist of (at least) looking in the mouth and listening to the heart and lungs with a stethoscope. An intravenous (IV) catheter will be placed, likely in the hand

or arm, and will remain in place throughout the study. Baseline vital signs will be obtained.

Subjects will be asked additional screening questions by the MRI scanner staff, per their protocol, to ensure that it is safe to undergo MRI scanning (no metal or electronic implants, no metal-containing tattoos, etc). Prior to entering the MRI environment, subjects will be asked to remove any jewelry, electronic, and glasses. In the unlikely event that their shirt contains metal, they will be provided a hospital gown and private space to change.

Subjects will then enter the scanner room, receive ear plugs and be connected to vital sign monitors, to measure your heart rate, blood pressure, and breathing (expired carbon dioxide). They will be connected to the IV lines and the crystalloid IV carrier fluid infusion will begin. From this point forward, regular vital signs will be obtained and documented, as would be done for a clinical anesthetic. The physician anesthesiologist will monitor the patient while they are receiving and recovering from the lidocaine infusion.

The experimental protocol consists of 3 basic elements: 4-minute battery of cognitive tasks (asynchronous with scanning), a functional MRI scan during a 4-minute block-design pain task consisting of five 10-second stimulations with 20 second rest periods, and an 8-minute resting-state (task-free) functional MRI scan. This will be performed first under just the IV fluid carrier infusion. Then, lidocaine will be administered, using a bolus+infusion strategy to reach steady-state effect-site target concentration of 1 mcg/ml. This level will be maintained for at approximately 20 minutes, while the above tasks/scans are obtained again under the low-dose lidocaine condition. When completed, an additional bolus and higher infusion rate of lidocaine will be administered to achieve an effect-site concentration of 1.5 mcg/ml. This level will be maintained for approximately 16 minutes, and the above three tasks/scans repeated under the high-dose lidocaine condition. Dosing schedules to achieve effect-site targets will be calculated on a per-subject basis using available modeling software and published pharmacokinetic models that account for sex, age, weight, and height. For reference, the total dose of lidocaine that would be administered to a prototypical 70 kg male subject would be <150 mg of lidocaine over the anticipated 40 minutes of infusion time. Structural (anatomical) scans will be obtained during transition periods of drug dosing, to minimize time exposed to the drug and time spent in the scanner. These needed scans for subsequent analysis are typically 4 minutes or less, and time needed for drug levels to reach steady state are similarly 6-7 minutes. Thus the total time spent in the scanner is anticipated to be less than 1 hour.

Subjects will then be removed from the scanner. Once sitting up, and after the resolution of any acute dizziness from moving through the magnetic field and/or the drug, they will be escorted to the adjacent recovery room. They will then be monitored by the anesthesiologist until fully recovered from the effects of sedation. Subjects will paid $150 during this recovery period. Once it is safe to do so, their IV will be removed

and they will be discharged from anesthesia care, anticipated to be <30 minutes after the end of scanning. Subjects will be reminded not to drive a vehicle or operate machinery after receiving lidocaine. There are no follow-up procedures. Subjects will be given the PI's contact information in the unlikely event that there are any late complications or questions after the study.

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References:

1. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures. Anesthesiology. 2017;126(3):376-93. doi: 10.1097/aln.0000000000001452.