LIMPP (Continuous Post-operative Lidocaine Infusion Following Major Reconstructive Spine Surgery in the Elderly to Minimize Delirium and Opiate Use: A Randomized Control Trial)

A randomized controlled trial to reduce postoperative delirium and opiate use through 48-hour postoperative lidocaine infusion in older surgical patients undergoing spinal surgery

Clinical trial number and registry URL: [Pending]

Version date: 03/31/2021

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University of California, San Francisco
PROTOCOL TEMPLATE

Instructions to User:

1. **Sections and text that are in regular font and that have not been highlighted in grey** represent standard language. In general, these sections should be present in your final protocol and the language should not be changed. However, every protocol is unique and changes to standard sections and language may be necessary to meet the needs of your protocol. Please review the language carefully to make sure that it is accurate for your study.
2. **Sections that are highlighted in grey, but that have regular font**, represent sections or information that needs to be customized as applicable to your study, but the language that is present is generally considered to be standard if that section (or procedure) applies to your protocol.
3. **Sections that are highlighted in grey, and where the text is italicized**, represent instructions with some example text. All require complete customization for your study.
4. As you customize each section of the protocol, **remove the highlighting and restore the font to regular (from italics)** to denote that section as having been completed.
5. When your protocol is complete, **review** it to ensure that all highlighting and italics have been removed.

This template protocol is based upon work supported in 2007 by the Cystic Fibrosis Foundation for the Therapeutics Development Network (TDN) and used with TDN Coordinating Center permission.

MARC BUREN

Clinical Research Protocol

A CLINICAL TRIAL OF POSTOPERATIVE LIDOCAINE INFUSION ON COGNITION AND OPIOID CONSUMPTION FOLLOWING MAJOR SPINE SURGERY

Protocol Number:	20-32383
Version Date:	11/23/2020
Investigational Product:	Lidocaine
IND Number:	N/A
Development Phase:	2
Sponsor:	Marc Buren Box 0648 Department of Anesthesia & Perioperative Care University of California, San Francisco 521 Parnassus Avenue, San Francisco, CA 94143-0730
Funding Organization:	N/A
Principal Investigator:	Name: Marc Buren Telephone: 314-374-9427 Fax: E-mail: marc.buren@ucsf.edu
Medical Monitor:	Name: Telephone: Fax: E-mail:
Coordinating Center:	If applicable

Approval:

	11/23/2020
PI or Sponsor Signature (Name and Title)	*Date*

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Dr. Marc Buren with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 20-32383

Protocol Title: Postoperative Lidocaine after Major Spine Surgery

Protocol Date: TBD

_____ _____

Investigator Signature *Date*

_____

Print Name and Title

Site # _____

Site Name _____

Address _____

_____

_____

_____

Phone Number _____

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Add all other abbreviations referenced in the protocol and delete any not referenced in the protocol.

AE	adverse event
CFR	Code of Federal Regulations
CRF	case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Hour
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
KG	Kilogram
MG	Milligram
PI	Principal Investigator
PK	pharmacokinetic
SAE	serious adverse experience

PROTOCOL SYNOPSIS

TITLE	A CLINICAL TRIAL OF POSTOPERATIVE LIDOCAINE INFUSION ON COGNITION AND OPIOID CONSUMPTION FOLLOWING MAJOR SPINE SURGERY
SPONSOR	Marc Buren
FUNDING ORGANIZATION	N/A
NUMBER OF SITES	1
RATIONALE	Spine procedures are a particularly painful class of surgery (1). Opioids are the mainstay of postoperative analgesic management, and while effective, often come with a host of significant side effects including a risk of delirium and altered cognition, dependence/addiction, respiratory depression, immune suppression, and gastrointestinal dysfunction (2). Lidocaine, an amide local anesthetic with class 1 antiarrhythmic, sedative, and anti-inflammatory properties has been increasingly utilized as part of a multi-modal anesthetic adjunct in a variety of surgical procedures (3-6). While there is literature that supports the use of postoperative infusions of lidocaine for additional benefits such as a decrease in opioid requirements, decreased hospital length of stay and faster return of bowel function, the data are limited in scope and quality (7-9). Additionally, there is essentially no data that has examined the effects of postoperative lidocaine on cognition. However, given the well described effects of opioids on cognition and delirium, we hope that if a postoperative infusion of lidocaine decreases opioid usage, it would then lead to a decreased risk of cognitive dysfunction (10-11) This pilot RCT will study a 48-hour postoperative infusion of lidocaine following major spine surgery to assess safety, and study the effects on opioid usage, delirium, and cognition.
STUDY DESIGN	Randomized, Double Blinded, Placebo Controlled
PRIMARY OBJECTIVE	To assess the safety and feasibility of using a postoperative infusion of lidocaine for the analgesic management of major spine surgery patients.

SECONDARY OBJECTIVES	To compare pain and the amount of opioid used postoperatively between the placebo vs. lidocaine infusion groups. To compare the incidence of postoperative delirium and cognitive dysfunction between the placebo and the lidocaine infusion group.
NUMBER OF SUBJECTS	60
SUBJECT SELECTION CRITERIA	Inclusion Criteria: •Major elective spine surgery patients (with instrumentation and fusion) with expected length of stay 3 days or greater •Spinal fusion > 2 levels •American Society of Anesthesiologists Classification Rating of 1-3 Age over 60 Exclusion Criteria: •Sensitivity or allergy to lidocaine. Significant heart disease •2nd or 3rd degree heart block-except when a pacemaker is in place. Severe cardiac failure (EF <30%), Adams-stokes, Wolff-Parkinson-White syndrome, or active dysrhythmia. •Stable atrial fibrillation/atrial flutter is not a contraindication. •Concurrent treatment with a class 1 antiarrhythmic (lidocaine, procainamide, propafenone, quinidine, disopyramide, phenytoin, flecainide) or amiodarone use <3 months. •Severe hepatic impairments (bili>1.46) Renal impairment (GFR <30) History of uncontrolled seizure Acute porphyria
TEST PRODUCT, DOSE, AND ROUTE	Intravenous Lidocaine at 1.33mg/kg/hr for a 48 hour infusion to begin in the post-anesthesia care unit.

OF ADMINISTRATION	
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Normal Saline at an equivalent rate to the comparable lidocaine dose (1.33mg/kg/hr) for a 48-hour infusion to begin in the post-anesthesia care unit.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on the study for the duration of their hospitalization, and at follow up in their surgeon's office. **Screening:** up to 7 days **Treatment:** 2 days (or duration of their hospital stay) **Follow-up:** 3 months (for data to be collected during surgical post-operative visit). The total duration of the study is expected to 12-24 months. 12-24 months for subject recruitment and 3 months for final subject follow-up.
CONCOMMITANT MEDICATIONS	Allowed: Standard postoperative analgesic meds as dictated by the surgical service. Prohibited: Ketamine Infusion
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• Difference in opioid usage between groups.
SECONDARY ENDPOINTS	• Difference in pain scores, incidence of cognitive dysfunction, functional status, and length of hospitalizations.
OTHER EVALUATIONS	N/A
SAFETY EVALUATIONS	Adverse events (AEs) will be graded by the principal investigator using the 0-5 point scale where 0 = no AE or within normal limits or not clinically significant, 1 = mild AE, did not require treatment, 2 = moderate AE, resolved with treatment, 3 = severe AE, resulted in inability to carry on normal activities and required professional medical attention, 4 = life threatening or disabling AE, and 5 = fatal AE The principal investigator will determine the relationship of AEs to the test study drug as one of the following: Not related, Possibly

	related, and Definitely related Description of Anticipated Adverse Events 1. Sedation – will be evaluated by the Richmond Agitation and Sedation Scale and also the "Analgesic sedation assessment form" developed by the Department of Clinical Pharmacy and Pharmaceutical Services at our institution. 2. Dizziness (self report) 3. Tinnitus or decreased hearing (self report) 4. Perioral Numbness or a metallic taste (self report) 5. Tremors (self report) Safety Data to be Evaluated The data that will be evaluated (after every ten patients enrolled) will include subjects' interview, vital signs, physical examination results, clinical test results such as creatinine, and postoperative analgesic dosages. All the above data will be evaluated by the PI. Additionally, functional status and neurocognitive data will be evaluated by the PI. Plan for Adverse Event Reporting All significant adverse events (both anticipated and unanticipated) will be reported to the following entities: University of California, San Francisco Committee on Human Research, National Institutes of Health, NIH Office of Biotechnology Activities (OBA), and Food and Drug Administration (if indicated) Events that may cause Termination/Drop out of a Participant from the Study: Adverse events (anticipated or unanticipated), Subject's unwillingness to continue with the study, Treating physician's request
PLANNED INTERIM ANALYSES	Given the limited scope of the present study, and small sample size. No interim analysis is planned.

STATISTICS **Primary Analysis Plan**	We will compare the VAS pain scores between the placebo and lidocaine groups using unpaired t-test. We will compare the amount of opioid used between groups using the unpaired t-test.
Rationale for Number of Subjects	This is a pilot RCT to help determine effect size and consider the safety of a lidocaine infusion. Published studies have shown a 50% decrease in opioid consumption when using a lidocaine infusion. Based on the average reduction and associated variance in those data, we should have an 80% chance to detect a 50% reduction at the 0.05% level of significance with a total sample size of 60 patients.

1 BACKGROUND

Lidocaine, an amide local anesthetic with class 1 antiarrhythmic, sedative, and anti-inflammatory properties has been increasingly utilized as part of a multi-modal anesthetic adjunct in a variety of surgical procedures (3-6). Infusions decrease postoperative opioid requirements, speed return of bowel function, and may decrease the risk of chronic post-surgical pain.

1.1 Overview of Non-Clinical Studies

N/A

1.2 Overview of Clinical Studies

Intravenous infusions of lidocaine have been used extensively during the intraoperative period, and while less common, have also been used postoperatively for the management of acute pain. Intraoperative dosing has utilized a variety of doses included boluses at the beginning of the procedure (typically with induction of anesthesia) that range from 1-2 mg/kg follow by infusions that range from 0.5-3 mg/kg/hr based on actual vs. lean vs. adjusted vs. ideal body weight.

Published data on posteroperative intravenous infusions of lidocaine for actue pain are much rarer. Prospective studies include Adair (2009) using 0.77mg/kg/hr and negative results for reduction in opioid usage. Lauwick (2009) using 1mg/kg/hr for 24 hours with positive results for clinically significant reduction in opioid consumption at 48 hours. Kaba (2009) used 1.3mg/kg/hr for 24 hours after laparoscopic colectomies, and showed a greater than 50% reduction of opioid consumption without any adverse results reported. Recently, De Oliveira (2020) reported retrospective results with infusions typically at 1mg/kg/hr for an average of 68 hours. In this cohort there were a total of 36 minor adverse events, and 1 serious adverse event requiring intervention.

In terms of cumulative effects there is conflicting evidence. Old data from LeLorier (1977) suggest that the elimination half-life increases after 24 hours to 3.22h from 100min in infusions less that 24 hours. More recent authors such at Eipe (2016) suggest that there is no accumulation over time. Additionally, the acute pain service at UCSF has significant experience with intravenous infusions for acute pain, and dose ranges are typically between 1-1.5mg/kg/hr, with an allowable dose of 2mg/kg/hr for 48 hours.

Based on the safety data from De Oliveira, the efficacy data from Kaba, and the data about plasma accumulation from LeLorier and Eipe and historical experience we have decided on an infusion of 1.33mg/kg/hr with close patient monitoring by a standardized nursing protocol and daily investigator questionnaires.

2 STUDY RATIONALE

Spine procedures are a particularly painful class of surgery. Opioids are the mainstay of postoperative analgesic management, and while effective, often come with a host of significant side effects including the risk of delirium and altered cognition,

dependence/addiction, respiratory depression, immune suppression, and gastrointestinal dysfunction.

Lidocaine, an amide local anesthetic with class 1 antiarrhythmic, sedative, and anti-inflammatory properties has been increasingly utilized as a part of a multi-modal anesthetic adjunct in a variety of surgical procedures. Infusions decrease postoperative opioid requirements, speed return of bowel function, and may decrease the risk of chronic post- surgical pain.

While there is literature that supports the use of postoperative infusions of lidocaine for additional benefits such as a decrease in opioid requirements, decreased hospital length of stay, and faster return of bowel function, the data are limited in scope and quality. Additionally, there is essentially no data that has examined the effects of postoperative lidocaine on cognition.

This small RCT will study a 48-hour postoperative infusion of lidocaine following major spine surgery to assess safety, and study the effects on opioid usage, delirium, and cognition following major spine surgery.

2.1 Risk / Benefit Assessment

1. We will carefully monitor the recruitment, enrollment and retention of study subjects.

2. We will exclude patients with a history of renal or hepatic dysfunction. Hepatic dysfunction will be assessed during a chart review for a known diagnosis of liver disease. Renal dysfunction will be based on the patient's preoperative renal function, which will be measured by serum creatinine levels and calculated glomerular filtration rate (GFR). Patients with a GFR <30 will be excluded.

The Cockroft and Gault Equation will be used to calculate creatinine clearance.

•Men Creatinine clearance = {140 – (age in yrs X weight in kg)}/ 72 X serum creatinine = mL/min

•For women, the value will be multiplied by 85%

3. We will monitor for all possible side effects related to the drugs which may include sedation, dizziness, tinnitus, perioral numbness, metallic taste, decreased hearing, slurred speech, tremors, cardiovascular issues, and GI problems. This will be assessed daily by either the PI or research assistant using the "Lidocaine Safety Questionnaire" form-see attachment. This will also be assessed by nursing according to the current order set protocol (every 2 hours for the first 4 hours, then every 4 hours for the duration of the infusion).

4 Adverse events will be monitored in real time for safety.

5. All study end-points will be closely defined to facilitate ease of monitoring.

3 STUDY OBJECTIVES

3.1 Primary Objective

To assess the safety and efficacy of using a postoperative intravenous infusion of lidocaine after major spine surgery in order to improve analgesic management.

3.2 Secondary Objectives

To assess the effect of a postoperative infusion of lidocaine on cognitive function and delirium following major spine surgery.

4 STUDY DESIGN

4.1 Study Overview

This is a prospective, double-blind, placebo-controlled study of 60 patients, >60 years of age, undergoing major spine surgery at the UCSF Medical Center. Patients will be randomized to receive either placebo (normal saline) or postoperative intravenous lidocaine, at 1.33mg/kg/hr, for 48 hours, starting upon arrival in the post-anesthesia care unit. Intraoperative anesthetic and other postoperative pain management strategies will be standardized. Postoperative delirium will be measured using structured interviews. Cognitive function will be measured using a battery of neurocognitive tests pre- and post-operatively. Using an intention to treat strategy, we will compare the amount of postoperative pain, opioid requirements, and postoperative delirium and cognitive dysfunction between the two groups. We will also assess any impact on length of stay, and functional outcome by comparing pre and postoperative results of the SF-36 and ODI.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

Primary efficacy endpoint will be a statistically significant reduction in opioid usage during the subject's hospitalization.

5.2 Secondary Efficacy Endpoints

Pain: Pain will be measured daily by the 11-point visual analog scale (0=no pain and 10=the worst possible pain) both at rest and with movement preoperatively and daily postoperatively for the first week. If the patient is in the hospital longer than 1 week after surgery, we will do a weekly evaluation until discharge. In addition, the site and treatment of pain, and the maximal level of pain experienced postoperatively will be measured. The measurement of pain is done routinely even if a subject does not enroll in the study.

Delirium: We will assess for delirium before surgery and after surgery daily for the first week. If the patient is in the hospital longer than 1 week after surgery, we will do a weekly evaluation until discharge. We will use the Confusion Assessment Method (CAM) (12) to determine the occurrence of delirium. This assessment tool was developed as a screening instrument based on the operationalization of DSM-III-R criteria for use by nonpsychiatric clinicians in high-risk settings. This method has a sensitivity of 94-100% and a specificity of 90-95% and has higher interobserver reliability (12), and has convergent agreement with four other mental status tests.

Lidocaine Safety: Tolerability and safety of lidocaine will be assessed according to the nursing protocol, which is part of the current lidocaine infusion order set. This protocol/order set was predetermined by acute pain service and predates this study. Patients will be assessed once per day by an investigator using a standardized script. The patient's labs will be monitored for lidocaine levels during their stay in the hospital on POD#1, POD#2 and the day after the infusion is complete (POD#3).

Functional Outcomes: Functional outcomes will be measured by comparing preoperative and postoperative scores on the Short-Form 36, Oswestry Disability Index (13). Both of these forms are collected by the spine clinic. Postoperative scores will be collected approximately 3 months after surgery at standard surgical follow-up visits.

5.3 Safety Evaluations

Adverse events (AEs) will be graded by the principal investigator using the 0-5 point scale where 0 = no AE or within normal limits or not clinically significant, 1 = mild AE, did not require treatment, 2 = moderate AE, resolved with treatment, 3 = severe AE, resulted in inability to carry on normal activities and required professional medical attention, 4 = life threatening or disabling AE, and 5 = fatal AE

The principal investigator will determine the relationship of AEs to the test study drug as one of the following: Not related, Possibly related, and Definitely related

Description of Anticipated Adverse Events

1. Sedation – will be evaluated by the Richmond Agitation and Sedation Scale and also the "Analgesic sedation assessment form" developed by the Department of Clinical Pharmacy and Pharmaceutical Services at our institution.

2. Dizziness (self report)

3. Tinnitus or decreased hearing (self report)

4. Perioral Numbness or a metallic taste (self report)

5. Tremors (self report)

- Safety Data to be Evaluated

The data that will be evaluated will include subjects' interview, vital signs, physical examination results, clinical test results such as creatinine, and postoperative analgesic dosages. All the above data will be evaluated by the PI. Additionally, functional status and neurocognitive data will be evaluated by the PI.

6 SUBJECT SELECTION

6.1 Study Population

Subjects presenting for major spine surgery who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

- Major elective spine surgery patients (with instrumentation and fusion) with expected length of stay 3 days or greater
    - Spinal fusion > 2 levels
- American Society of Anesthesiologists Classification Rating of 1-3
- Age over 60

1. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

1. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
2. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
3. Sensitivity or allergy to lidocaine.
4. Significant heart disease

    a. 2nd or 3rd degree heart block-except when a pacemaker is in place.
    b. Severe cardiac failure (EF <30%),
    c. Adams-stokes, Wolff-Parkinson-White syndrome, or active dysrhythmia.
        - Stable atrial fibrillation/atrial flutter is not a contraindication.
    d. Concurrent treatment with a class 1 antiarrhythmic (lidocaine, procainamide, propafenone, quinidine, disopyramide, phenytoin, flecainide) or amiodarone use <3 months.

5. Severe hepatic impairments (bili>1.46)
6. Renal impairment (GFR <30)
7. History of uncontrolled seizure
8. Acute porphyria

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy following major spine surgery is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

Postoperative intravenous infusion of ketamine.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Patients enrolled in the study will be randomized to one of the two study groups, either intervention or placebo, using block randomization.

8.2 Blinding

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or patients. The following study procedures will be in place to ensure double-blind administration of study treatments.

- Access to the randomization code will be strictly controlled.
- Packaging and labeling of test and control treatments will be identical to maintain the blind.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the Investigator should discuss the emergency with the Medical Monitor prior to unblinding.

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

The study drug is lidocaine, and the placebo will be normal saline. Both are standard formulations provided by the UCSF pharmacy. Both are colorless liquids of similar viscosity. The pharmacy obtains lidocaine from various manufacturers.

8.3.2 Formulation of Control Product

0.9% Saline will be the control product

8.3.3 Packaging and Labeling

Study medications will be supplied by the UCSF pharmacy. Study drug and placebo will be placed in a 500ml intravia bag by pharmacy.

8.4 Supply of Study Drug at the Site

Medication is standard formulation supplied by UCSF pharmacy.

8.4.1 Dosage/Dosage Regimen

Intravenous lidocaine dose will be 1.33 mg/kg/hr based on adjusted body weight as a continuous infusion for 48 hours upon arrival in the post-anesthesia care unit.

8.4.2 Dispensing

Drug will be dispensed by the pharmacy.

8.4.3 Administration Instructions

MDs will have access to a study specific ERX (Apex drug order). Medication will be delivered as a continuous intravenous infusion without any change in rate for 48 hours.

8.5 Supply of Study Drug at the Site

Drug is supplied by the UCSF pharmacy

8.5.1 Storage

No special storage requirements once dispensed by the pharmacy. Both study medication and placebo are stable at normal room temperatures.

8.6 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.7 Measures of Treatment Compliance

Treatment compliance will be monitored by checking the patients MAR and daily visits.

9 STUDY PROCEDURES AND GUIDELINES

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented on the day of surgery. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be obtained from apex.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases will be obtained from apex.

9.1.4 Delirium/Cognitive Function

Incident delirium present in any of the first three postoperative days will be the secondary outcome. Delirium will be measured preoperatively and daily on the first three postoperative days by trained research assistants using the Confusion Assessment Method (CAM), a screening instrument based on the Diagnostic and Statistical Manual-III-R criteria and was validated by health care providers. (1) Patients will be considered to be delirious if the CAM assessment reveals acute onset or fluctuating course of mental status change, inattention, and either disorganized thinking or altered level of consciousness. If a CAM assessment is missing for any of the three days post-surgery, delirium will be determined from the patient's medical record in accordance with the chart-based CAM delirium identification method developed by Inouye *et al*. (2)·(3)

In addition to measuring incident postoperative delirium on any of the first three days, we will also measure the severity of delirium using the Memorial Delirium Assessment Scale (MDAS). (4)

Cognitive function will be measured by a battery cognitive tests used commonly in our UCSF IRB approved studies. These include the digit symbol substitution test, (5) the timed verbal fluency test, (6) and the word list learning task (7) in order to assess the cognitive domains of memory and learning (word list), verbal and language skills (verbal fluency), attention, concentration, and perception (digit symbol test). For each test, we will determine whether the patient experience a significant decline from preoperative baseline using prediction intervals. (8) A decline from preoperative performance of 4 or more points for the word list, or 7 or more points for the verbal fluency and the digit symbol tests will be considered significant decline and the subject will be classified as having POCD for that day. If decline in performance is observed for at least one postoperative day, we will conclude that POCD occurs for that patient. (9) The above scores were determined in earlier studies of community living older adults similar in demographic and clinical characteristics to the subjects in this study, but who had not undergone an intervention that could cause cognitive change.(10-12) In addition to the above tests, cognitive status will also be measured preoperatively using the Telephone Interview of Cognitive Status instrument (TICS)(13) which was adapted from the Mini

Mental Status Examination. The TICS allows us to evaluate the baseline cognitive status of patients but patients will not excluded based on the TICS values.

9.1.5 Functional Outcomes

Functional outcomes will be measured by comparing preoperative and postoperative scores on the Short-Form 36, Oswestry Disability Index (13). Both of these forms are collected by the spine clinic. Postoperative scores will be collected approximately 3 months after surgery at standard surgical follow-up visits.

9.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the Serious Adverse Events (SAE) report form

9.1.7 Sleep/Pain Assessment

Pain will be measured daily by the 11-point visual analog scale (0=no pain and 10=the worst possible pain) both at rest and with movement preoperatively and daily postoperatively for the first week. If the patient is in the hospital longer than 1 week after surgery, we will do a weekly evaluation until discharge. In addition, the site and treatment of pain, and the maximal level of pain experienced postoperatively will be measured. The measurement of pain is done routinely even if a subject does not enroll in the study.

Sleep Quality and quantity will be measured daily using a questionnaire including duration or sleep, number of awakenings, daytime somnolence, need for pharmaceutical adjuncts, and subjective assessment of quality.

9.1.8 Lidocaine Safety

Tolerability and safety of lidocaine will be assessed according to the nursing protocol, which is part of the current lidocaine infusion order set. This protocol/order set was predetermined by acute pain service and predates this study. Patients will be assessed once per day by an investigator using a standardized script.

10 EVALUATIONS BY VISIT

10.1 Visit 1 (1-7 days prior to scheduled Surgery)

1. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Perform Initial Delirium Screening

10.2 Visit 2 (POD#0-7)

Daily visits will record the information listed below

1. Ensure Patient is receiving study medication or has had study medication discontinued according to the protocol
2. Administer Lidocaine Safety Questionnaire
3. Administer Sleep/Pain Assessment
4. Administer CAM for delirium assessment.

10.3 Visit 3 (Surgical Clinic Follow Up)

1. Patient completes standard post-surgical follow-up health forms including SF-36 and ODI at the surgeon's clinic. This usually takes place 1-3 months following surgery.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity

- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (identified via medical records review)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.3 Replacement of Subjects

Subjects who withdraw from the study treatment will be replaced.

Subjects who withdraw from the study will be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Early termination of study drug
- Incorrect administration of study drug (as administered by pharmacy)
- Escalation of pain management protocol to include ketamine
- Additional surgery during study period
- Failure to obtain informed consent prior to study procedures.
- Failure to administer clinical assessments relating to safety, pain, and delirium during study period.

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 DATA SAFETY MONITORING

The UCSF Data Safety Monitoring Board (DSMB) will establish a Data Monitoring Committee (DMC) to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study, according to the UCSF Data Safety Monitoring Board Operations Manual and a DMC

Charter to be established for this protocol. There will not be an interim review conducted by the DMC given the limited trial size and daily safety monitoring already conducted.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

15.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: race, gender, age, height, weight, ASA status, medical conditions, preoperative opioid use, location and extent of planned procedure.

15.3 Analysis of Primary Endpoint

We will compare the VAS pain scores between the placebo and lidocaine groups using unpaired t-test. We will compare the amount of opioid used between groups using the unpaired t-test.

15.4 Analysis of Secondary Endpoints

Safety and tolerability data will be summarized by treatment group.

We will compare the incidence of side effects between the placebo and lidocaine groups using the chi-squared test.

We will compare the incidence of postoperative delirium and cognitive dysfunction between the two groups using the chi-square test. Multivariate logistic regression will be used to determine the independent predictive value of the use of lidocaine on postoperative delirium and cognitive dysfunction.

The data will be analyzed locally at UCSF.

Detailed methods of VAS pain measurements, opioid doses, and cognitive function assessment will be described in the other sections.

15.5 Sample Size and Randomization

This is a pilot RCT to help determine effect size and consider the safety of a lidocaine infusion. Published studies have shown a 50% decrease in opioid consumption when using a lidocaine infusion. Based on the average reduction and associated variance in

those data, we should have an 80% chance to detect a 50% reduction at the 0.05% level of significance with a total sample size of 60 patients.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug. These data will be recorded on various forms as detailed in other sections of this protocol.

Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of all data collection forms will remain at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into a validated database. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.4 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND

has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.5 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.6 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.