CLINICAL PROTOCOL

CAFFEINE AND NEUROLOGIC RECOVERY FOLLOWING SURGERY AND GENERAL ANESTHESIA

Study Agents: Caffeine Citrate

HUM #: 00135919

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PROTOCOL SYNOPSIS

Study Title: Caffeine and Neurologic Recovery Following Surgery and General Anesthesia

Study Phase: Phase II

Primary Objective: The objective is to establish feasibility of perioperative caffeine administration in relation to targeted postoperative neurologic outcomes

Study Design: Randomized, triple-blinded, controlled trial with a 1:1 allocation ratio (placebo: caffeine) in a two-arm parallel design

Study Population: Adult (≥18 years old) patients undergoing non-cardiac, non-neurologic, non-major vascular surgery at a tertiary university hospital

Diagnosis and Main Criteria for Inclusion

Each subject must meet the following criteria to be enrolled in this study:

• Adult surgical patients (≥18 years old)
• Non-cardiac, non-neurologic, non-major vascular surgery (i.e., below the diaphragm)

Subjects who meet any of the following criteria will be excluded from study:

• Emergency surgery
• Severe cognitive impairment
• Uncontrolled cardiac arrhythmia history
• Seizure disorder history
• Preoperative opioid use
• Pheochromocytoma
• Caffeine sensitivity/allergy
• Conflicting research study enrollment
• Acute liver failure
• Pregnancy
• Breastfeeding
• Severe audiovisual impairment
• Non-English speaking
• History of diabetes

Test Product; Dose; and Mode of Administration: Caffeine citrate 60 mg/mL (30 mg/mL caffeine). Proposed dose 200 mg caffeine, 40 mL dilution, 60-min IV infusion.

Reference or Placebo Therapy; Dose; and Mode of Administration: 40 mL 5% dextrose in water intravenous infusion over 60 minutes.

Duration of Treatment: 60-minute intravenous infusion

Variables: Postoperative opioid consumption, postoperative pain scores, time to anesthetic emergence, new sleep disturbances, electroencephalographic markers of brain recovery, postoperative cognitive function testing, depression/anxiety/affect scores, and perioperative caffeine use.

Statistical Methods: The analysis will be longitudinal with repeated oral morphine equivalent (OME) measurements i.e. we will analyze multiple points of the OME curve simultaneously. A generalized linear mixed model will be the primary analytic tool with appropriate data-driven choice of the link function.. Power calculations reveal >80% power to detect difference by a two-sided t-test with unequal variances.

1 INTRODUCTION

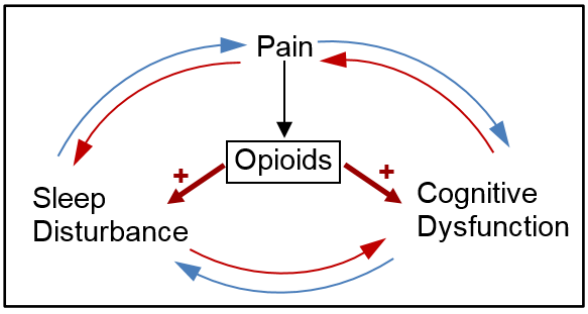
1.1 Indication

Pain and cognitive dysfunction remain common and distressing complications after surgery. For example, approximately 75% of patients report moderate/severe pain after surgery,[1] and cognitive dysfunction can persist for months after non-cardiac surgery.[2] Furthermore, these outcomes are interrelated, as pain itself may worsen cognitive function,[3,4] leading to further overall neurologic impairment. Unfortunately, there are few novel, neurobiologically informed strategies available to pre-emptively address such deleterious outcomes. Although opioids remain a mainstay therapy for managing postoperative pain, opioids can induce cognitive dysfunction,[5] sleep disruption,[6,7] and persistent postoperative use.[8]

1.2 Background and Rationale

Over 300 million surgical procedures are performed each year worldwide,[9] the majority with general anesthesia. Many fundamental questions in the fields of neuroscience and anesthesiology persist, such as the relationship between pain and arousal state perturbations. Evidence suggests a neurobiologic pain-arousal state connection, such that pain, sleep disturbance, and cognitive dysfunction may interact in a synergistic, reciprocating manner (Figure 1).[4,10-13] In clinical practice, these adverse pain-arousal state interactions are often ineffectively addressed, and surgical patients are particularly vulnerable to entering this refractory cycle given the pain and brain state alterations associated with surgical interventions. In fact, 75% of surgical patients report moderate-to-severe pain after surgery,[1] nearly 50% of patients report sleep disturbances perioperatively,[13] and up to 70% of patients experience cognitive dysfunction after surgery.[14,15] Acute postoperative pain and cognitive dysfunction are also associated with negative outcomes, such as increased hospital length of stay,[16] persistent opioid use,[8] and prolonged cognitive decline.[17,18] Opioids remain a mainstay therapy for treating acute surgical pain, but opioids also interfere with sleep architecture[6,7] and cognitive function,[5,19,20] further propagating the deleterious cycle of pain-arousal state perturbation (Figure 1).

Figure 1: Sleep disturbance, pain, and cognitive dysfunction are reciprocally related.



Preliminary data from our laboratory research group demonstrate that caffeine, a non-selective adenosine receptor antagonist, demonstrates both acute anti-nociceptive properties and protection against postoperative pain in both sleep-deprived and non-sleep-deprived rat models.[21] In fact, recent systematic reviews found that caffeine provided significant analgesic benefit as part of a multimodal strategy in both surgical[22] and non-surgical settings.[23] Caffeine also augments electroencephalographic (EEG) signs of arousal,[24] and it has been shown to improve cognitive function in a variety of settings.[25] Nonetheless, caffeine is not routinely given perioperatively, and whether caffeine facilitates such neurocognitive arousal after surgery, and how such brain state modulation may impact postoperative pain and opioid requirements, remains unknown.

1.3 Hypothesis

The central hypothesis is that intraoperative caffeine administration will improve opioid consumption, pain, and neuropsychological recovery in patients undergoing surgery.

1.4 Previous Human Experience

Caffeine has been safely used for decades for various clinical indications. Pertinently, caffeine has long track record of safe and effective use in adult surgical and obstetric patients for post-dural puncture/post-operative pain. A targeted literature review is provided below:

Derry et al., 2015 (Cochrane review):[22] The objective of this review was to assess the analgesic efficacy and safety of oral ibuprofen plus caffeine for postoperative pain. The number needed to treat for achieving at least 50% maximum pain relief was 2.1 (95% confidence interval, 1.8-2.5) to 2.4 (1.9-3.1). Adverse event rates were similar between placebo and ibuprofen-caffeine groups, and no serious adverse events or withdrawals were reported due to the ibuprofen-caffeine combination.

Basurto Ono et al., 2015 (Cochrane review):[26] The objective of this review was to assess the effectiveness and safety of drugs used for treating post-dural puncture headache. Caffeine was found to be a safe, effective intervention for reducing headache pain in both post-partum and non-obstetric surgery patients. No clinically significant adverse events were reported related to caffeine.

Derry et al., 2014 (Cochrane review):[23] The objective was to assess relative efficacy of caffeine for acute pain, with surgical patients included as part of a diverse array of clinical settings (i.e., surgical and non-surgical). Significant pain relief was appreciated at doses ≥ 100 mg, and no significant adverse events were reported related to caffeine.

Steinbrook et al., 2013:[27] The goal of this study was to determine if caffeine sodium benzoate (500 mg) reduced the incidence of postoperative nausea and vomiting (primary outcome). Caffeine was not found to reduce postoperative nausea and vomiting. In fact, more patients randomized to caffeine reported nausea in the PACU (26% vs. 10%,

respectively, p=0.02), though there was no significant difference in vomiting, rescue antiemetics used, or nausea/vomiting over 24 hours. No other adverse events were reported.

Zeger et al., 2012:[28] prospective, double-blinded randomized trial (N=16, caffeine arm) conducted in the emergency room for postdural puncture headache. Intravenous caffeine (500-1000 mg) infused over 60 minutes/dose, 80% effective (95% CI 60-100%) for treating headache pain. No adverse events were reported.

Yucel et al., 1999:[29] prospective, double-blinded randomized trial (N=30, caffeine arm) conducted with orthopedic surgery patients. 500 mg caffeine-sodium benzoate (250 mg caffeine) infused over 90 minutes, significant improvement in post-spinal headache. No adverse events or side effects were reported.

Weber et al. 1997:[30] this prospective, randomized, double-blinded trial examined caffeine efficacy in relation to postoperative headache and recovery time. Caffeine was found to significantly reduce postoperative headache compared to placebo (10% vs. 23%, respectively, $p<0.05$) in patients at risk for withdrawal symptoms.

Camann et al., 1990:[31] prospective, double-blinded, randomized trial (N=20, caffeine arm) conducted with postpartum patients. Oral formulation of caffeine (300 mg). Significant improvement noted in spinal headaches. No significant side effects reported with caffeine therapy. 1/20 patients (5%) complained of mild/transient flushing and jitteriness after receiving caffeine, though this was the same proportion in the placebo group (5%).

Jarvis et al., 1986:[32] exploratory study, letter to the editor (N=18) – 500 mg caffeine-sodium benzoate (250 mg caffeine) infused over 60 minutes, second dose if necessary. Significant relief in 14/18 (75%) of patients. No adverse events or significant side effects were reported.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

- **A. Measure postoperative pain outcomes in surgical patients receiving caffeine compared to placebo.**

  As described above, laboratory data from our research team demonstrate that preoperative caffeine administration blunted postoperative pain for up to six postoperative days.[21] *We hypothesize that caffeine will improve postoperative pain outcomes*. Cumulative opioid consumption will be measured during the first postoperative week, and validated pain measures (e.g., visual analog scale [VAS], behavioral pain scale [BPS]), will be used to assess postoperative inpatient pain scores.

- **B. Compare the clinical effects of caffeine and placebo on neurocognitive recovery from general anesthesia in surgical patients.**

  Given that caffeine has been found to accelerate anesthetic recovery in laboratory models,[33] reduce low-frequency electroencephalographic (EEG) power,[24,34,35] and improve cognitive performance across a variety of settings,[25] *we also hypothesize that caffeine administration will accelerate neurocognitive recovery following surgery and anesthesia.* Our team will calculate anesthetic emergence time, characterize EEG patterns during emergence and recovery, and perform cognitive function testing in the postanesthesia care unit (PACU). We will use the validated Trail Making Test (TMT), which provides information on psychomotor speed, visual scanning, mental flexibility, and executive function.[36] Such testing will be suitable for the PACU setting..

- **C. Compare the clinical effects of caffeine and placebo on neuropsychological recovery after surgery.**

  Depression has been identified as an independent risk factor for opioid dependence in surgical patients, and caffeine is also associated with reduced risk of depression.[37] Thus, *we also hypothesize that caffeine will improve mood and reduce signs of depression postoperatively.* Symptoms of depression will be assessed using the Hospitalized Anxiety and Depression Scale (HADS),[38] and affect will be characterized using the Positive and Negative Affect Schedule (PANAS).[39] To differentiate acute cognitive disorders (i.e., hypoactive delirium) from symptoms of depression, the Confusion Assessment Method (CAM) will be used to assess for delirium using our group's previously described methods.[14,40] We will also administer the Quality of Recovery (QoR) Score in patients post-operatively. This strategy will provide a more comprehensive assessment of the effects of caffeine on postoperative neuropsychological recovery.

2.2 Endpoints

2.2.1 Primary Endpoint

Cumulative opioid consumption (mg) through postoperative day 3 (or discharge, whichever is sooner.

*2.2.2 Secondary Endpoint**

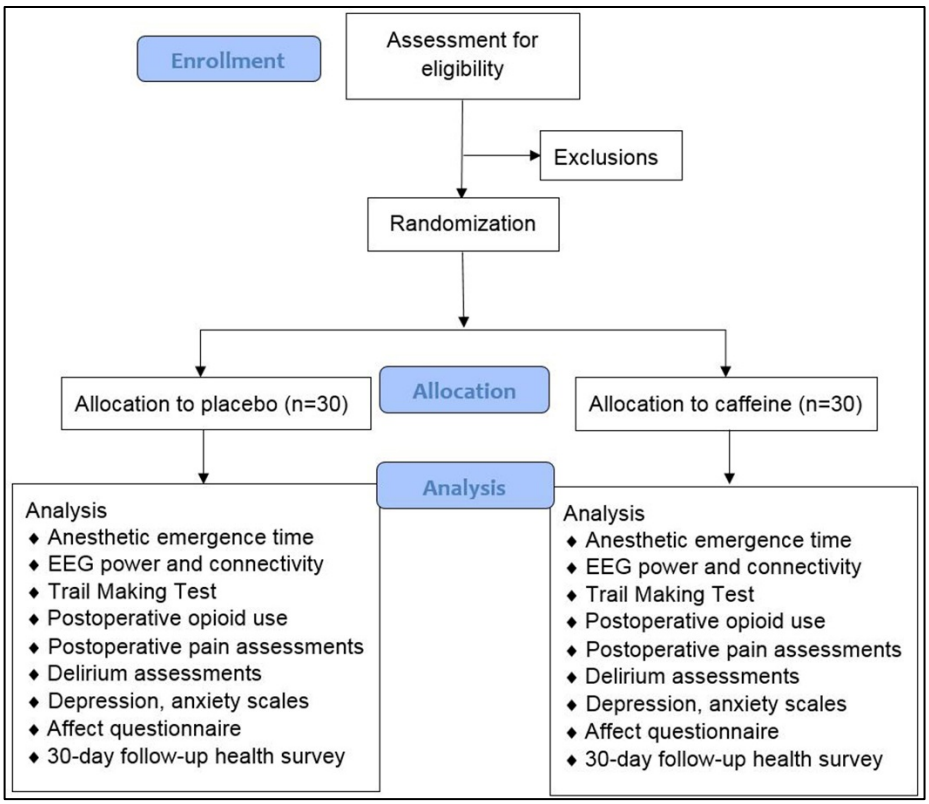
- VAS, n, PACU and postoperative days 1-3 (twice daily)
- BPS, n, PACU and postoperative days 1-3 (twice daily)
- Time until anesthetic emergence (min)
- Delirium incidence (%)
- Positive depression screen incidence (%)
- Positive anxiety screen incidence (%)
- Change in affect scores (n)
- Change in Trail Making Test scores (n) from baseline

Tertiary assessments are listed in section 7.2

3 STUDY DESIGN

This will be a single-center, triple-blinded, randomized controlled trial at the University of Michigan Health System, and approval has been obtained from the University Michigan Medical School IRB. The overall study flow is presented in the CONSORT[41] Flow Diagram (Figure 2). As with our past studies, patients will be recruited at preoperative clinics, where informed consent will be obtained. Randomization methods will follow a stratified randomization model to match patients based on age and gender. Participants will be randomized with a 1:1 allocation ratio (placebo: caffeine) in a two-arm parallel design, and the randomization schedule and coding will be held by our hospital research pharmacy. Prepared intravenous piggyback solutions of 5% dextrose in water or caffeine citrate (200 mg caffeine) will be directly delivered to the operating room prior to the surgery of enrolled participants. The dose of 200 mg was chosen for two reasons: (1) this dose is in-line with similar clinical neurophysiology studies involving caffeine[34,35,42,43] and (2) this has been the intraoperative dose used for safely preventing post-dural puncture/post-operative pain in surgical and obstetric patients.[22,29,32] In these studies, no significant side effects or adverse events were reported in relation to caffeine. This study will fulfill CONSORT guidelines[41] for clinical trials as outlined in the following sections. Furthermore, this trial will be registered with www.clinicaltrials.gov prior to trial initiation, and all study team members will be certified in Good Clinical Practice as outlined by the NIH.

Figure 2: Planned study flow diagram based on Consolidated Standards of Reporting Trials (CONSORT)



Planned study flow diagram based on Consolidated Standards of Reporting Trials (CONSORT).[41]
EEG = electroencephalogram

Inclusion criteria: Adult (≥18 years old) patients undergoing non-cardiac, non-neurologic, non-major vascular surgery (i.e., below the diaphragm).

Exclusion criteria: Emergency surgery, cognitive impairment precluding capacity for informed consent, uncontrolled cardiac arrhythmias, seizure disorders, intolerance or allergy to caffeine, history of diabetes, preoperative opioid use, pheochromocytoma, acute liver failure, enrolled in conflicting research study, pregnancy, breastfeeding, severe visual or auditory impairment (may hinder cognitive function testing), and patients unable to speak English.

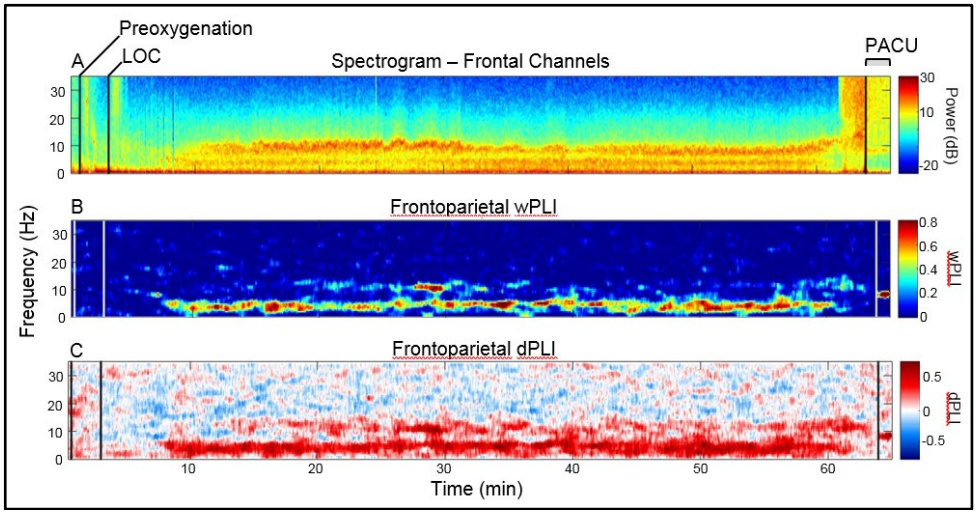
Perioperative and anesthetic procedures: Patients will be consented and enrolled at preoperative clinic locations, where a medical and psychiatric history will be taken and baseline assessments will be administered (described further below). After enrollment, patients will also complete a caffeine intake survey to quantify baseline caffeine consumption. On the day of surgery, baseline cognitive function testing (TMT) will take place in the preoperative holding area. Subsequently a 16-channel wireless EEG system (Cognionics, Inc.) will be applied to the scalp for continuous monitoring during surgery and the perioperative period. Once in the operating room, anesthetic induction and maintenance will proceed as deemed clinically appropriate by the anesthesia team. At the beginning of surgical closure, the study drug will be given via intravenous infusion over 60 minutes (placebo vs. caffeine, 200 mg) in a triple-blinded fashion: the anesthetic team, research staff, and patient will all be blinded to the intervention. Infusion of this dose over a 60-minute period has been safely described, without significant side effects or adverse events noted.[28,32] A member of the research team will remain in the operating room to monitor drug infusion and collect data regarding timing of anesthetic discontinuation and emergence; this will aid methodological rigor and data validation for the study. The EEG sensors will remain in place during the operation and emergence from anesthesia; they will then be removed shortly after PACU arrival. One hour after the caffeine infusion finishes, pain and cognitive function measures will be assessed.

Pain and sleep assessments: Inpatient opioid consumption will be monitored from the first PACU assessment through postoperative day three (or discharge, whichever occurs sooner) (primary outcome). Subacute opioid consumption (postoperative days 4-7) will be calculated as an additional outcome. All opioids will be converted to oral morphine equivalents (mg), and intraoperative opioid administration will be calculated as well and compared between groups. Pain measures will include the 10 centimeter Visual Analog Scale (VAS)[44] and Behavioral Pain Scale (BPS)[45] for subjective and objective pain assessment, respectively. Assessments will begin 1 hour after caffeine infusion has finished (once patient is in the PACU), and they will continue twice daily (morning and afternoon) for the first three postoperative days. Preoperatively, the Richards-Campbell Sleep Questionnaire (RCSQ)[46] will be administered to determine self-reported sleep quality the previous evening. As an additional outcome, self-reported sleep disturbances will also be assessed during these daily pain assessments (i.e., from the PACU through postoperative day 3).

EEG data acquisition: Our research group has extensive experience with EEG data acquisition and analysis in human volunteers[47,48] and surgical patients.[49,50] We have

demonstrated feasibility with collecting whole-scalp, 16-channel wireless EEG data (Cognionics, Inc.) in 50 surgical patients. Representative spectral and connectivity data are presented in Figure 3. Our group will use this same EEG technology to collect and analyze data for the proposed study. Spectral power (decibels, DB) and connectivity (phase lag index, PLI) data will be collected and analyzed during anesthetic emergence and PACU arrival.

Figure 3: Representative wireless EEG data from a surgical patient



Example wireless perioperative EEG data obtained from a related study (R01GM098578). LOC = loss of consciousness, PACU = postanesthesia care unit, dB = decibels, PLI = phase lag index (an EEG measure of functional connectivity).

Neurocognitive assessments: Time from surgical closure to anesthetic emergence will be calculated by the study team. (minutes). The Trail Making Test will be used to assess perioperative cognitive function. The TMT is a validated, reliable test that assesses four cognitive domains relevant to the perioperative setting: processing speed, attention, visual scanning, executive function, and working memory.[36] The TMT is administered in a standardized fashion using paper and pencil and takes approximately 5 minutes to complete. This is a feasible strategy in the perioperative setting to obtain comprehensive cognitive function data (e.g., attention, executive function) in a relatively short period of time, and normalized population data are available for comparisons.[36] The test will be administered preoperatively and one hour after the caffeine infusion has completed in conjunction with pain assessments. Changes (n) in standardized scores from baseline will be calculated, and final standardized scores (n) will also be calculated and reported in the event that baseline scores are unable to be obtained (given the time-constraints present in the preoperative setting, it might not be possible to achieve baseline cognitive function scores in all patients).

Neuropsychological assessments: The *Hospital Anxiety and Depression Scale (HADS)*[38] will be used to assess for active depression and anxiety symptoms in each group. These assessments will take place at baseline and after the last inpatient assessment on postoperative day 3. Scores ≥8 for the anxiety (HADS-A) and depression (HADS-D) subscales will be considered positive screens.[51] The *Positive and Negative Affect Schedule*

(PANAS)[39] will be used to characterize mood and affect at the same time points as depression and anxiety screening (baseline and postoperative day 3). The *Confusion Assessment Method (CAM)* will be used to assess for delirium throughout the first three postoperative days using previously described methods.[14,40] Lastly, a follow-up health and well-being survey will be sent to participants thirty days after surgery. This survey will include the Veterans RAND 12 Item Health Survey (VR-12, continuous measure).[52] Presence of persistent opioid use (yes/no, binary) will also be asked in this thirty-day survey.

4 SUBJECT SELECTION

4.1 Subject Recruitment

4.1.1 Inclusion Criteria

1. Adult surgical patients (≥18 years of age)
2. Non-cardiac surgery
3. Non-major neurologic surgery (e.g., non-intracranial, non-major spine)
4. Non-major vascular surgery (i.e., below the diaphragm)

4.1.2 Exclusion Criteria

1. Emergency surgery
2. Severe cognitive impairment precluding capacity for informed consent
3. Uncontrolled cardiac arrhythmias
4. Seizure disorder history
5. Intolerance or allergy to caffeine
6. Preoperative opioid use
7. Pheochromocytoma
8. Enrolled in conflicting research study
9. Patients in acute liver failure
10. Pregnancy
11. Breastfeeding
12. Severe audiovisual impairment
13. Non-English speaking

5 STUDY TREATMENTS

5.1 Allocation to Treatment

Participants will be block randomized with a 1:1 allocation ratio (placebo: caffeine) in a two-arm parallel design, and the randomization schedule and coding will be held by our hospital research pharmacy. Prepared intravenous piggyback solutions of 5% dextrose in water (placebo) or caffeine citrate (200 mg caffeine) will be directly delivered to the operating room prior to the surgery of enrolled participants.

5.2 Breaking the Blind

The randomization can be broken, if necessary, per the physicians caring for the subject to ensure subject safety. With the exception medical emergency, the blind will only be broken by the PI.

5.3 Drug Supplies

5.3.1 Formulation, Preparation and Dispensing

Parenteral drug products should and will be inspected visually for particulate matter prior to administration whenever solution and container permit. Per manufacturer (Fresenius Kabi USA, LLC) package insert: Caffeine citrate injection is indicated for the short-term treatment of apnea of prematurity in infants between 28 and < 33 weeks gestational age.

Caffeine citrate injection, USP for intravenous administration is a clear, colorless, sterile, nonpyrogenic, preservative-free, aqueous solution adjusted to pH 4.7. Each mL contains 20 mg caffeine citrate (equivalent to 10 mg of caffeine base) prepared in solution by the addition of 10 mg caffeine anhydrous to 5 mg citric acid monohydrate, 8.3 mg sodium citrate dihydrate and Water for Injection. Caffeine, a central nervous system stimulant, is an odorless white crystalline powder or granule, with a bitter taste. It is sparingly soluble in water and ethanol at room temperature. The chemical name of caffeine is 3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione. In the presence of citric acid it forms caffeine citrate salt in solution.

Caffeine citrate is supplied via vials that contain 3mL of solution at a concentration of 20 mg/mL caffeine citrate (60 mg/vial) equivalent to 10 mg/mL caffeine base (30 mg/vial).

5.3.2 Drug Storage and Drug Accountability

Caffeine citrate injection, USP (NDC 63323-407-03), is stored at 20-25 degrees Celsius (68-77 degrees Fahrenheit) in 3 mL single-dose vials. The drug will be stored in the hospital research pharmacy in accordance with hospital pharmacy practice and guidelines.

5.4 Concomitant medications

No other study drugs will be given. Participants will receive medications as clinically indicated by perioperative providers.

6 STUDY PROCEDURES

6.1 Screening Visit

For initial screening visits, patients will be seen during preoperative clinic visits. The study coordinator will review the study details with potential participants, and informed consent will be obtained after confirming eligibility criteria are met. Depending on when a preoperative clinic visit is scheduled in relation to surgery, the timeframe from enrollment to drug administration may vary significantly (days-to-weeks). The goal will be to recruit patients whose surgeries are scheduled for the morning, so as to minimize the likelihood of administering caffeine late in the afternoon. See "Schedule of Activities" for full list of procedures that will occur at this visit and all subsequent visits. Assessments, testing, and measures are described in detail in the above "Study Design" section.

6.2 Treatment Study Period

6.2.1 Visit 1 (Day 1)

As outlined in the above protocol, visit 1 (day 1) will be the day of scheduled surgery. During this time, a preoperative pregnancy test will first be drawn as clinically indicated. Vitals will be taken throughout the perioperative period per clinical guidelines and protocols. The RCSQ will be administered to assess sleep quality the prior evening. Baseline Trail Making Test (TMT) scores will be collected. The wireless EEG cap will then be placed preoperatively, and EEG monitoring will then commence perioperatively under supervision of the study team. A member of the study team will then receive the study drug from the research pharmacy, which will prepare the drug per block randomization protocol. The study team will then administer this during (one-hour infusion) at the beginning of surgical closure. The EEG cap will be removed after postanesthesia care unit (PACU) arrival, and one hour after the infusion has finished, the study team will perform the designated research study assessments (i.e., pain assessments, cognitive function testing, and Quality of Recovery (QoR) questionnaire). Intraoperative and PACU opioid data will also be tabulated.

6.2.2 Visits 2 – 4 (Postoperative Days 1-3)

Morning and afternoon pain (VAS, BPS), delirium, sleep disturbance, and caffeine intake assessments will be taken. Opioid consumption will be calculated during this time, and adverse events will also be recorded. Vitals will be recorded per clinical protocol on each respective ward/ICU. On postoperative day one, QoR will be collected. On postoperative day three, follow-up inpatient HADS and PANAS assessments will take place to assess depression, anxiety, and affect.

6.2.3 Follow-up (Postoperative Days 4-7)

During this time, opioid consumption and caffeine intake assessments will be obtained over the telephone. Adverse events will continue to be monitored.

SCHEDULE OF ACTIVITIES

Protocol Activity	Screen	Visit 1 Day 1 *Day of Surgery*	Visit 2 Day 2 *POD1*	Visit 3 Day 3 *POD2*	Visit 4 Day 4 *POD3*	Phone call Days 5-7 *POD4-7*	Day 30
Visit (POD1-3) /Phone call (POD4-7)	**-**	**X**	**X**	**X**	**X**	**X**	
Informed consent	X						
Medical history	X						
Vitals*	X	X	X	X	X		
Depression, Anxiety, and Affect Scales	X			X			
Serum pregnancy test		X					
Randomization		X					
Treatment with study agent		X					
Opioid use assessments		X	X	X	X	X	
Cognitive function testing	X	X[†]					
Pain/sleep assessments[‡]	X	X	X	X	X		
Caffeine intake assessment	X		X	X	X	X	
EEG assessments		X					
Adverse event assessment		X	X	X	X	X	
Health and well-being survey							X

* Vitals will be recorded per clinical protocol on each respective ward/ICU. [†]Second cognitive function testing session will occur in the postanesthesia care unit. [‡]Pain and sleep assessments will occur and twice daily (morning and afternoon) from POD1-3; the RCSQ in particular will be administered on Day 1, preoperatively. Pain assessments will also be taken once in the postanesthesia care unit prior to the cognitive function assessment. POD = postoperative day, TMT = trail making test, EEG = electroencephalogram

7 ASSESSMENTS

7.1 Primary Endpoint Assessments

Cumulative opioid consumption (mg) – through first three postoperative days

7.2 Secondary and Tertiary Assessments

Secondary Outcomes

•VAS scores (n)

•BPS scores (n)

•Time to anesthetic emergence (min)

•Change in TMT scores (n)

•Delirium incidence (%)

•Postoperative depression screen incidence (%)

•Postoperative anxiety screen incidence (%)

•Change in affect scores (n)

Tertiary Outcomes

•EEG spectral power (decibels, dB)

•EEG connectivity (e.g., phase lag index, PLI)

•Daily number of caffeinated beverages (n) – to compare overall caffeine intake between the two groups throughout the study period (as a potential confounding/mediating variable).

•Preoperative sleep quality, via Richards-Campbell Sleep Questionnaire (continuous measure, n) as a potential confounding/mediating variable.

•New self-reported sleep disturbances (n) in each group

•Opioid use (mg), postoperative days 4-7

•Opioid use (yes/no) at 30 days

•Patients-reported health and well-being scores (n) – Veterans RAND 12 Item Health Survey (VR-12, continuous measure)[52] at 30 days

8 ADVERSE EVENT REPORTING

Adverse Event Definition
An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

These events may be:

a. *Definitely related:* clearly associated with study drug/treatment
b. *Probably related*: likely associated with study drug/treatment
c. *Possibly related*: may be associated with study drug or other treatment
d. *Unlikely to be related*, or
e. *Definitely not related* to the study drug/treatment

For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of following criteria are met:

a. There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.
b. There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.
c. The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.
d. A potential alternative cause does not exist.

Serious Adverse Events (SAE): An adverse drug experience occurring at any dose that results in any of the following outcomes:

a. Death
b. A life-threatening adverse drug experience
c. Inpatient hospitalization or prolongation of existing hospitalization
d. A persistent or significant disability &/or incapacity
e. A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose.
Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon

appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

Expected adverse events are those adverse events that are listed in the protocol, the study drug labeling or in the study informed consent document.

Unexpected adverse events are those that:

a. are not described in the labeling as far as the study drug is concerned.
b. are not anticipated in the study informed consent. This includes adverse events for which the specificity or severity is not consistent with the description in the informed consent.

Unanticipated problem: Per FDA Procedural Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009), A serious problem that has implications for the conduct of the study (requiring a significant and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent or investigator's brochure).

Unanticipated problem Reporting: Per 21 CFR 312.66, 312.53 (c)(1)(vii), and 56.108(b)(1), should an Unanticipated problem occur during the investigation, the investigator will promptly report all unanticipated problems involving risks to human subjects or others to IRBMED /FDA.

The severity or grade of an adverse event may be measured using the following definitions:

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve.

Event reporting: The study will comply with the IRB & FDA reporting requirements and guidelines.

9 DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

Sample size and power analysis is based on opioid consumption data observed in 102 hysterectomy patients treated at the University of Michigan with patient heterogeneity with respect to CNS involvement in the pain processing summarized by the Fibromialgia Survey score (FM). Acute opioid responses on POD1 varied between 0.7 and 6.5 (mean OME) with the standard deviation varying 3-18, dependent on the tertile of the FM score. Based on these data we hypothesize that caffeine affecting the pain processing system can show a difference as large as 0.7 vs. 6.5 with standard deviations of 3 and 10, respectively. This will give us the power of 83%, with a sample size of 60, to detect the difference by a two-sided t-test with unequal variances. We note that the opioid consumption distribution is of exponential type and therefore sample means, while approximately normal are a rather crude summary of the difference in the OME distribution by group. We therefore consider the above calculation conservative. The expected reserves of power attained through the use of the appropriate longitudinal model (see Analysis of Primary Endpoint) will be used to lend more power to secondary regression and causal analyses involving explanatory variables and potential mediators. We expect a ~10% drop-out rate, and will continue recruitment until the full 71 patients have been recruited (after drop-out).

9.2 Data Analysis

9.2.1 Analysis Populations

All analyses will come from the same surgical population (adults ≥ 18 years of age, presenting for major non-cardiac, non-neurologic, non-vascular surgery).

9.2.2 Exploratory Data Analysis (EDA)

Exploratory Data Analysis (EDA) techniques such as histograms, QQ-Plots, box-plots, scatterplots and basic descriptive (means, medians, IQR) will be used to assess the distribution of dependent measures. These will be used to identify the distribution of outcomes which in turn will be conductive to determining the appropriate analysis strategies. In addition, these techniques will also be used to explore the most informative transformations of the covariates, confounders and relevant predictors considered in the analysis. Extreme values will be determined and their removal from the analysis will be determined. Missing patterns and rates will be assessed. However, missing data for the primary outcome are unanticipated given the availability of inpatient medication administration records. If patterns and MAR and rates are <20%, complete case analysis will be considered. If rates are >20% multiple imputation techniques will be used to complete the data. All variables included in the analysis (outcome, covariates, predictors, confounders) as well as other auxiliary variables should be included in the imputation process. In addition, multicollinearity will be assessed using Pearson's correlation coefficient and Variance Inflation Factor (VIF) analysis. Predictors with VIF>10 will not be included in the multivariable models.

Potential selection bias will be investigated comparing demographics, confounders and relevant predictors by caffeine used and by days. Unbalanced distributions of confounders and relevant predictors will be determined with standardized differences (SD). Measures with SD>0.1 will be included in the multivariable models.

9.2.3 Analysis of Primary Endpoint

A generalized linear mixed model will be the primary analytic tool with appropriate data-driven choice of the link function. Linear regression will be used for assessing cumulative opioid consumption through postoperative day three. A separate analysis will entail longitudinal modeling with repeated oral morphine equivalent (OME) measurements (i.e., we will analyze multiple points of the OME curve simultaneously). A Gaussian subject-specific intercept term will be included to model between-subject differences and the associated correlation structure. The Time variable (main effect, baseline, PACU, POD1-3) will be used to model the pattern of the respective outcome variable (response) over time in the placebo group. The Group variable (an indicator of the caffeine group, main effect) is an indicator of whether the subject received the caffeine intervention. The Group by Time interaction term expresses the differences of caffeine vs. placebo as far as the pattern of response over time is concerned. Final results will be assessed based on the best model selected using Likelihood Ratio tests and Akaike Information Criteria (AIC). In addition to the model specified above, a models will be constructed a) containing the above group and time specification with the addition of demographic variables and b) containing (a) with the addition of intraoperative factors.

9.2.4 Analysis of Secondary Endpoints

For secondary endpoints, continuous data will be analyzed using Student's t-test or Mann-Whitney U test, as appropriate. Categorical data will be analyzed using chi-squared or Fisher's Exact tests, as appropriate. Modeling will be performed similar to the above primary endpoint description if appropriate.

10 MONITORING

10.1 Data Safety and Monitoring Plan (DSMP)

Our team will adhere to institutional IRB protocols for reporting adverse events and performing scheduled reviews across the proposed study. Our research team will also meet weekly to discuss any issues that may arise. All participants will be monitored throughout the entire perioperative course by both the research team (including direct PI oversight) and clinical teams per routine care. Participants will also have phone and pager numbers to the study coordinator and the study PI if any concerns arise. Finally, all protocols and consent forms are approved by the University of Michigan Medical School IRB and are reviewed yearly, per IRB guidelines.

11 DATA HANDLING AND RECORD KEEPING

11.1 CRFs / Electronic Data Record

Electronic data will be de-identified and stored online using the REDCap electronic research database, which is managed by the Michigan Institute for Clinical and Health Research (our NIH-funded clinical-translational science institute) Data Management Core. The REDCap online database resides on a secured, password-protected network managed by the Michigan Institute of Clinical and Health Research.

11.2 Record Retention

Per 21 CRF §312.62, study records will be retained for 2 years after the investigation is discontinued.

12 ETHICS

12.1 IRB/FDA

An IND Exemption request will be submitted to the FDA. The study will also be reviewed and approved by the Institutional Review Board (IRBMED, University of Michigan, Ann Arbor, MI).

This study will be carried out in compliance with the protocol and in accordance with the ethical principles that are consistent with the principles of Good Clinical Practice and in compliance with other applicable regulatory requirements., as described below:

14. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

15. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

16. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

12.2 Institutional Review Board (IRB)

Before implementing this study, the protocol, the proposed informed consent form and other information to be provided to subjects, must be reviewed by a properly constituted Institutional Review Board (IRB). Any amendments to the protocol must be reviewed and approved by IRBMED.

12.3 Subject Information and Consent

The study team member will explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and will be submitted for IRB approval.

12.4 STUDY DISCONTINUATION CRITERIA

12.4.1 Stopping Rules for Safety reasons

Including, but not limited to, the following reasons:

•Participant is found to not meet all eligibility criteria after enrollment

•Adverse cardiac event (e.g., unstable arrhythmia) noted with drug infusion

•Adverse neurologic event (e.g., seizure) noted with drug infusion

•Clinician caring for the patient has requested discontinuing of the study due to safety concerns

As outlined above, the study team will also review all adverse events and make additional decisions regarding the continuation or discontinuation of the study, as appropriate.

12.4.2 Rules for Discontinuation of a Subject

In additions to the reasons cited above, participants may voluntarily discontinue study participation at any time. In the event a patient drops out of the study or is discontinued due to protocol violations, all attempts will be made to exit the patient in accordance with the protocol requirements.

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